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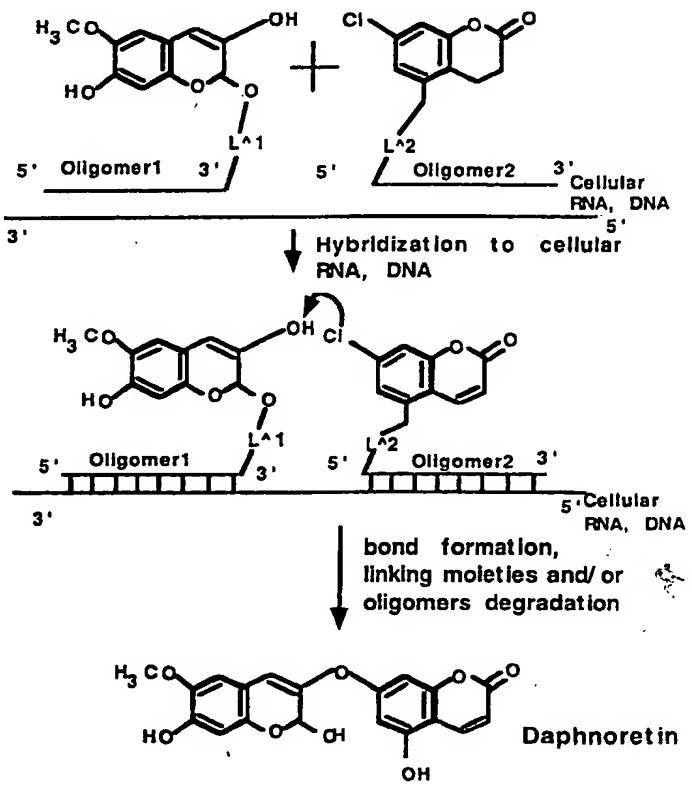
(54) Title: SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS IN CELLS

(57) Abstract

This invention relates to a new method of synthesis of biologically active substances of determined structure directly in the cells of living organisms containing specific RNA or DNA molecules of determined sequence. The method is based on the hybridization of two or more oligomers bound with biologically inactive precursors of biologically active substances to specific RNA or DNA in vivo in the cells of living organisms. After hybridization of the oligomers to RNA or DNA the biologically inactive precursors bound to the 5' and/or 3' ends of the oligomers can interact with each other to make biologically active form of the substances. This changing of properties is due to chemical reactions which bind the biologically inactive precursors through a chemical bond into a biologically active form of the whole compound.



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Synthesis of biologically active compounds in cells.

Technical field

Int.Cl......**C07F 9/22**; C07F 9/28;
C07C 321/00; C07C 323/00
U.S. Cl. **560/147**; 562/9; 562/10; 562/11
Field of search..... **C07F 9/22**; C07F 9/28;
C07C 321/00; C07C 323/00

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Background Art.

The use of oligo(ribo)nucleotides and their analogues as anticancer and antiviruses theraupetic agents was first proposed several years ago. (Uhlmann, 1990) The great number of different modifications of the oligonucleotides and the methods of their use has since been developed.

Two basic interactions between oligonucleotides and nucleic acids are known (Moser and Dervan, 1987)

1. Watson-Crick base pairing (Duplex structure)
2. Hoogsten base pairing (Triplex structure)

Oligonucleotides can form duplex and/or triplex structures with DNA or RNA of cells and so regulate transcription or translation of genes.

It has been proposed that different substances, which can cleave target nucleic acids or inhibit important cellular enzymes could be coupled to oligomers. The use of such conjugates as therapeutic agents has been described.(USA patent, 5,177,198; 5,652,350).

Other methods are based on the coupling of different biologically active substances, such as toxins, to monoclonal antibodies which can then recognise receptors or other structures of cancer cells, or cells infected with viruses. Monoclonal antibodies can then specifically recognise cancer cells and in this way transport toxins to these cells. But these methods are inefficient due to the high level of non-specific interactions between antibodies and other cells, which leads to delivery of the toxins or other biologically active compounds to the wrong cells.

In 1979 I.M. Klotz and co-authors proposed a method for complementary carrier peptide synthesis based on a template-directed scheme (J.A. Walder et al. 1979). The method proposed the synthesis of peptides on a solid support using unprotected amino acids, and the subsequent hybridization of oligonucleotides on the template. This method was established only for synthesis of peptides in vitro using solid supports of a different origin, and involved many synthesis steps to obtain peptides of the determined structure.

M. Masuko and co-authors proposed another method for in vitro detection of specific nucleic acids by excimer formation from two pyrene-labeled probes (Ebata, K. et al. 1995).

My invention allows the synthesis of different BACs of determined structure directly in living organisms only in cells, which have specific RNA or DNA sequences. In this way, BACs will be delivered only to those cells where specific nucleic acids are produced.

Disclosure of Invention

Definitions

"mononucleomer"

The term "mononucleomer" means a "Base" chemically bound to "S" moieties. Mononucleomers can include nucleotides and nucleosides such as thymine, cytosine, adenine, guanine, diaminopurine, xanthine, hypoxanthine, inosine and uracil. Mononucleomers can bind each other to form oligomers, which can be specifically hybridized to nucleic acids in a sequence and direction specific manner.

The "S" moieties used herein include D-ribose and 2'-deoxy-D-ribose. Sugar moieties can be modified so that hydroxyl groups are replaced with a heteroatom, aliphatic group, halogen, ethers, amines, mercapto, thioethers and other groups. The pentose moiety can be replaced by a cyclopentane ring, a hexose, a 6-member morpholino ring; it can be amino acids analogues coupled to base, bicyclic riboacetal analogues, morpholino carbamates, alkanes, ethers, amines, amides, thioethers, formacetals, ketones, carbamates, ureas, hydroxylamines, sulfamates, sulfamides, sulfones, glycinyl amides other analogues which can replace sugar moieties. Oligomers obtained from the mononucleomers can form stabile duplex and triplex structures with nucleic acids.(Nielsen P.E. 1995, U.S.pat.No 5,594,121).

"Base"

"Base" (designated as "Ba") includes natural and modified purines and pyrimidines such as thymine, cytosine, adenine, guanine, diaminopurine, xanthine, hypoxanthine, inosine, uracil, 2-aminopyridine, 4,4-ethanocytosine, 5-methylcytosine, 5-methyluracil, 2-aminopyridine and 8-oxo-N(6)-methyladenine and their analogues. These may include, but are not limited to adding substituents such as -OH, -SH, -SCH(3), -OCH(3), -F,-Cl,-Br, -

NH(2), alkyl, groups and others. Also, heterocycles such as triazines are included.

"Nucleotide"

Nucleotide as used herein means a base chemically bound to a sugar or sugar analogues having a phosphate group or phosphate analog.

"oligomer"

Oligomer means that at least two "mononucleomers" (defined above) are chemically bound to each other. Oligomers can be oligodeoxyribonucleotides consisting of from 2 to 200 nucleotides, oligoribonucleotides consisting of from 2 to 200 nucleotides, or mixtures of oligodeoxyribonucleotides and oligoribonucleotides. The mononucleomers can bind each other through phosphodiester groups, phosphorothioate, phosphorodithioate, alkylphosphonate, boranophosphates, acetals, phosphoroamidate, bicyclic riboacetal analogues morpholino carbamates, alkanes, ethers, amines, amides, thioethers, formacetals, ketones, carbamates, ureas, hydroxylamines, sulfamates, sulfamides, sulfones, glycinyl amides and other analogues which can replace phosphodiester moiety. Oligomers are composed of mononucleomers or nucleotides. Oligomers can form stable duplex structures via Watson-Crick base pairing with specific sequences of DNA, RNA, mRNA, rRNA and tRNA in vivo in the cells of living organisms or they can form stable triplex structures with double stranded DNA or dsRNA in vivo in the cells of living organisms.

"Alkyl"

"Alkyl" as used herein is a straight or branched saturated group having from 1 to 10 carbon atoms. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl and the like.

"Alkenyl"

"Alkenyl" as used herein is a straight- or branched-chain olefinically-unsaturated group having from two to 25 carbon atoms. The groups contain from one to three double bounds.

Examples include vinyl (-CHdbdCH(2), 1-propenyl (-CHdbdCH-CH(3)), 2-methyl-1-propenyl (-CHdbdC(CH(3))-CH(3)) and the like

"Alkynyl"

"Alkynyl" as used herein is a straight or branched acetynically-unsaturated group having from two to 25 carbon atoms. The groups contain from one to three triple bounds. Examples include 1-alkynyl groups include ethynyl (-CtbdCH), 1-propynyl (-CtbdC-CH(3)), 1-butynyl (-CtbdC-CH(2 -CH(3)), 3-methyl-butynyl (-CtbdC-CH(CH(3))-CH(3)), 3,3-dimethyl-butynyl (-CtbdC-C(CH(3))(3)), 1-pentynyl (-CtbdC-CH(2, -CH(2 -CH(3)) and 1,3-pentadiynyl (-CtbdC-CtbdC-CH(3)) and the like.

"Aryl"

"Aryl" as used herein includes aromatic groups having from 4 to 10 carbon atoms. Examples include phenyl, naphtyl and like this.

"Heteroalkyl"

"Heteroalkyl" as used herein is an alkyl group in which 1 to 8 carbon atoms are replaced with N (nitrogen), S (sulfur) or O (oxygen) atoms. At any carbon atom there can be one to three substituents. The substituents are selected from: -OH, -SH, -SCH_3, -OCH_3, halogen, -NH_2, NO_2, -S(O)-, -S(O)(O)-, -O-S(O)(O)-O-, -O-P(O)(O)-O-, -NHR and -R. Here R is alkyl, alkenyl, aryl, heteroaryl, alkynyl, heterocyclic, carbocyclic and like this groups.

"Heteroalkenyl"

"Heteroalkenyl" as used herein is an alkenyl group in which 1 to 8 carbon atoms are replaced with N (nitrogen), S (sulfur) or O (oxygen) atoms. At any carbon atom there can be one to three substituents. The substituents are selected from group -OH, -SH, -SCH_3, -OCH_3, halogen, -NH_2, NO_2, -S(O)-, -S(O)(O)-, -O-S(O)(O)-O-, -O-P(O)(O)-O-, -NHR and -R. Here R is alkyl, alkenyl, aryl, heteroaryl, alkynyl, heterocyclic, carbocyclic and like this groups.

"Heteroalkynyl"

"Heteroalkynyl" as used herein is an alkynyl group in which 1 to 8 carbon atoms are replaced with N (nitrogen), S (sulfur) or O (oxygen) atoms. At any carbon atom there can be one to three substituents. The substituents are selected from group -OH, -SH, $-SCH_3$, $-OCH_3$, halogen, $-NH_2$, NO_2, -S(O)-, -S(O)(O)-, -O-S(O)(O)-O-, -O-P(O)(O)-O-, -NHR. Here R is alkyl, alkenyl, aryl, heteroaryl, alkynyl, heterocyclic, carbocyclic and like this groups.

"Heteroaryl"

"Heteroaryl" as used herein means an aromatic radicals comprising from 5 to 10 carbon atoms and additionally containing from and to three heteroatoms in the ring selected from group S, O or N. The examples include but not limited to: furyl, pyrrolyl, imidazolyl, pyridyl indolyl, quinolyl, benzyl and the like. One to three carbon atoms of aromatic group can have substituents selected from -OH, -SH, $-SCH_3$, $-OCH_3$, halogen, $-NH_2$, NO_2, -S(O)-, -S(O)(O)-, -O-S(O)(O)-O-, -O-P(O)(O)-O-, -NHR, alkyl group. Here R is alkyl, alkenyl, aryl, heteroaryl, alkynyl, heterocyclic, carbocyclic or similar groups.

"Cycloheteroaryl"

"Cycloheteroaryl" as used herein means a group comprising from 5 to 25 carbon atoms from one to three aromatic groups which are combined via a carbocyclic or heterocyclic ring. An illustrative radical is fluorenylmethyl. One to two atoms in the ring of aromatic groups can be heteroatoms selected from N, O or S. Any carbon atom of the group can have substituents selected from -OH, -SH, $-SCH_3$, $-OCH_3$, halogen, $-NH_2$, NO_2, -S(O)-, -S(O)(O)-, -O-S(O)(O)-O-, -O-P(O)(O)-O-, -NHR, alkyl group. Here R is alkyl, alkenyl, aryl, heteroaryl, alkynyl, heterocyclic and carbocyclic and like this groups.

"Carbocyclic"

"Carbocyclic" as used herein designates a saturated or unsaturated ring comprising from 4 to 8 ring carbon atoms. Carbocyclic rings or groups include cyclopentyl, cyclohexyl and

phenyl groups. Any carbon atom of the group can have substituents selected from -OH, -SH, $-SCH_3$, $-OCH_3$, halogen, $-NH_2$, NO_2, -S(O)-, -S(O)(O)-, -O-S(O)(O)-O-, -O-P(O)(O)-O-, -NHR, alkyl group and R. Here R is alkyl, alkenyl, aryl, heteroaryl, alkynyl, heterocyclic and carbocyclic and like this groups.

"Heterocyclic ring"

"Heterocyclic ring" as used herein is a saturated or unsaturated ring comprising from 3 to 8 ring atoms. Ring atoms include C atoms and from one to three N, O or S atoms. Examples include pyrimidinyl, pyrrolinyl, pyridinyl and morpholinyl. At any ring carbon atom there can be substituents such as -OH, -SH, $-SCH_3$, $-OCH_3$, halogen, $-NH_2$, NO_2, -S(O)-, -S(O)(O)-, -O-S(O)(O)-O-, -O-P(O)(O)-O-, -NHR, alkyl. Where R is alkyl, alkenyl, aryl, heteroaryl, alkynyl, heterocyclic and carbocyclic and like this groups.

"Hybridization"

"Hybridization" as used herein means the formation of duplex or triplex structures between oligomers and ssRNA, ssDNA, dsRNA or dsDNA molecules. Duplex structures are based on Watson-Crick base pairing. Triplex structures are formed through Hoogsteen base interactions. Triplex structures can be parallel and antiparallel.

The word "halogen" means an atom selected from the group consisting of F (fluorine), Cl (clorine), Br (bromine) and I (iodine)

The word "hydroxyl" means an --OH group.

The word "carboxyl" means an -- COOH function.

The word "mercapto" means an -- SH function.

The word "amino" means --NH(2) or --NHR. Where R is alkyl, alkenyl, aryl, heteroaryl, heteroalkyl, alkynyl, heterocyclic, carbocyclic and like this groups.

"Biologically active compounds (BACs)"

"Biologically active compound as defined herein include but are not limited to:

1) biologically active peptides and proteins consisting of natural amino acids and their synthetic analogues L, D, or DL configuration at the alpha carbon atom selected from valine, leucine, alanine, glycine, tyrosine, tryptophan, tryptophan

isoleucine, proline, histidine, lysin, glutamic acid, methionine, serine, cysteine, glutamine phenylalanine, methionine sulfoxide, threonine, arginine, aspartic acid, asparagin, phenylglycine, norleucine, norvaline, alpha-aminobutyric acid, O-methylserine, O-ethylserine, S-methylcysteine, S-benzylcysteine, S-ethylcysteine , 5,5,5-trifluoroleucine and hexafluoroleucine. Also included are other modifications of amino acids, which include but are not limited to, adding substituents at carbon atoms such as -OH, -SH, $-SCH_3$, $-OCH_3$, -F,-Cl,-Br, $-NH_2$. The peptides can be also glycosylated and phosphorylated.

2) Cellular proteins which include but are not limited to: enzymes, DNA polymerases, RNA polymerases, esterases, lipases, proteases, kinases, transferases, transcription factors, transmembrane proteins, membrane proteins, cyclins, cytoplasmic proteins, nuclear proteins, toxins and like this.

3) Biologically active RNA such as mRNA, ssRNA, rsRNA and like this.

4) Biologically active alkaloids and their synthetic analogues with added substituents at carbon atoms such as -OH, -SH, $-SCH_3$, $-OCH_3$, -F,-Cl,-Br, $-NH_2$, alkyl straight and branched.

5) Natural and synthetic organic compounds which can be:

a) inhibitors and activators of the cellular metabolism;

b) cytolitical toxins;

c) neurotoxins;

d) cofactors for cellular enzymes;

e) toxins;

f) inhibitors of the cellular enzymes.

"Precursor(s) of biologically active substances (PBAC(s))"

"Precursors of biologically active compounds (**PBACs**)" as used herein are biologically inactive precursors of BACs which can form whole BACs when bound to each other through chemical moiety(ies) "m" or simultaneously through chemical moieties "m" and "m^1". "m" and "m^1" are selected independently from: -S-S-, -O-, -NH-C(O)-, -C(O)-NH-, -C(O)-, -NH-, dbdN-, -C(O)O-, -C(O)S-, -S-, -C(S)S-, -C(S)O-, -N=N-.

Biologically active peptides and proteins are synthesized from shorter biologically inactive peptides. These shorter peptides as used herein are also biologically inactive precursors of biologically active compounds.

Biologically active RNAs can be synthesized from biologically inactive oligoribonucleotides.

"oligomer-PBAC"

"Oligomer-**PBAC**" as used herein means a precursor of a BAC (**PBAC**) which is chemically bound at the first and/or last mononucleomer at the 3' and/or 5' ends of the oligomer through the chemical moieties L^1 and/or L^2. Chemical moieties L^1 and L^2 can be bound directly to a base or to a sugar moiety or to sugar moiety analogues or to phosphates or to phosphate analogues,

"oligomer$_n$-PA$_n$"

"Oligomer$_n$-PA$_n$" as used herein means the precursor of a biologically active protein or RNA which is chemically bound at the first and/or last mononucleomer at the 3' and/or 5' ends of the oligomer through the chemical moieties L^1 and/or L^2. n means the ordinal number of the oligomer of PA. PAs are biologically inactive peptides or biologically inactive oligoribonucleotides. Wherein n is selected from 2 to 300.

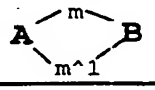
a) In Formulas from 1 to 4 **PBAC**s are designated as "**A**" and "**B**".

A-m-B is equal to a whole BAC "**T**"

"m" is selected independently from -S-S-, -O-, -NH-C(O)-, -C(O)-NH-, -C(O)-, -NH-, dbdN-, -C(O)O-, -C(O)S-, -S-, -C(S)S-, -C(S)O-, -N=N-.

A-O-**B**	is equal to a whole BAC	"**T**"
A-NH-C(O)-**B**	is equal to a whole BAC	"**T**"
A-C(O)-NH-**B**	is equal to a whole BAC	"**T**"
A-C(O)-**B**	is equal to a whole BAC	"**T**"
A-NH-**B**	is equal to a whole BAC	"**T**"
A-dbdN--**B**	is equal to a whole BAC	"**T**"
A-C(O)O-**B**	is equal to a whole BAC	"**T**"
A-C(O)S-**B**	is equal to a whole BAC	"**T**"
A-C(S)S-**B**	is equal to a whole BAC	"**T**"
A-S-S-**B**	is equal to a whole BAC	"**T**"
A-C(S)O-**B**	is equal to a whole BAC	"**T**"
A-N=N-**B**	is equal to a whole BAC	"**T**"

b) Biologically active compounds can be formed through moieties "m" and "m^1". "m" and "m^1" are selected independently from: -S-S-, -O-, -NH-C(O)-, -C(O)-NH-, -C(O)-, -NH-, dbdN-, -C(O)O-, -C(O)S-, -S-, -C(S)S-, -C(S)O, -N=N-, so that



is equal to biologically active compound "T"

a BAC is represented on figure 4.

c) In Formulas from 5 to 7, precursors of BACs (**PBACs**) are designated as "**PA**$_n$", where n is selected from 2 to 300. "**PA**" are peptides consisting of from 2 to 100 amino acids or oligoribonucleotides consisting of from 2 to 50 ribonucleotides. {**PA**$_1$-m-**PA**$_2$-m-**PA**$_3$-m-...-m-**PA**$_{n-3}$-m-**PA**$_{n-2}$-m-**PA**$_{n-1}$-m-**PA**$_n$} is equal to BAC. BACs in this case are proteins or RNAs. Proteins can be enzymes, transcription factors, ligands, signaling proteins, transmembrane proteins, cytolitical toxins, toxins, cytoplasmic proteins, nuclear proteins and the like.

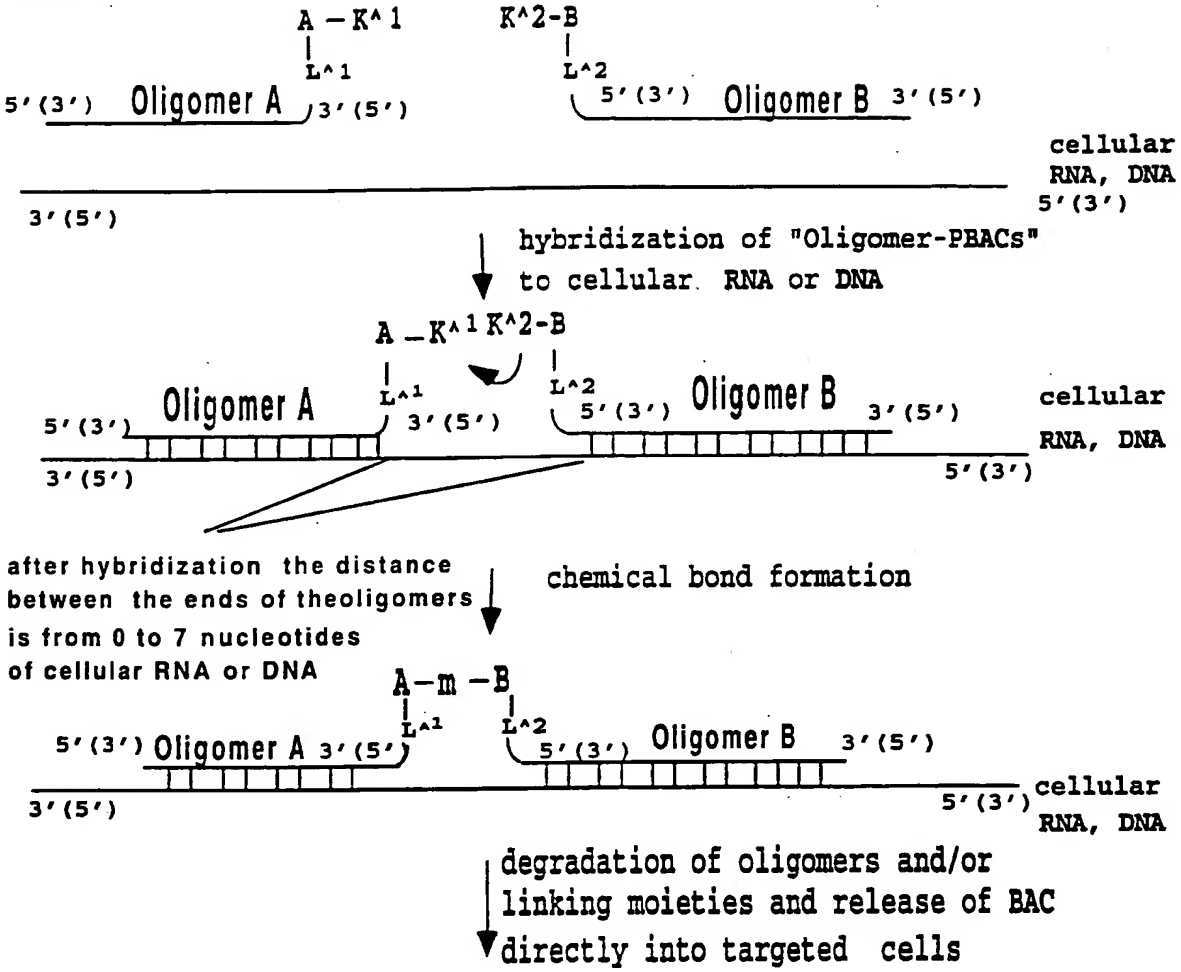
Detailed disclosure of the invention

This invention relates to the synthesis of biologically active compounds directly into the cells of living organisms. This is achieved by the hybridization of two or more oligomers to cellular RNA or DNA. These oligomers are bound to biologically inactive PBACs (oligomer-PBACs) containing chemically active groups.

BAC can be synthesized only in those cells of living organisms which have specific RNA or DNA molecules of a determined sequence.

The principle Formulas of the invention are represented below:

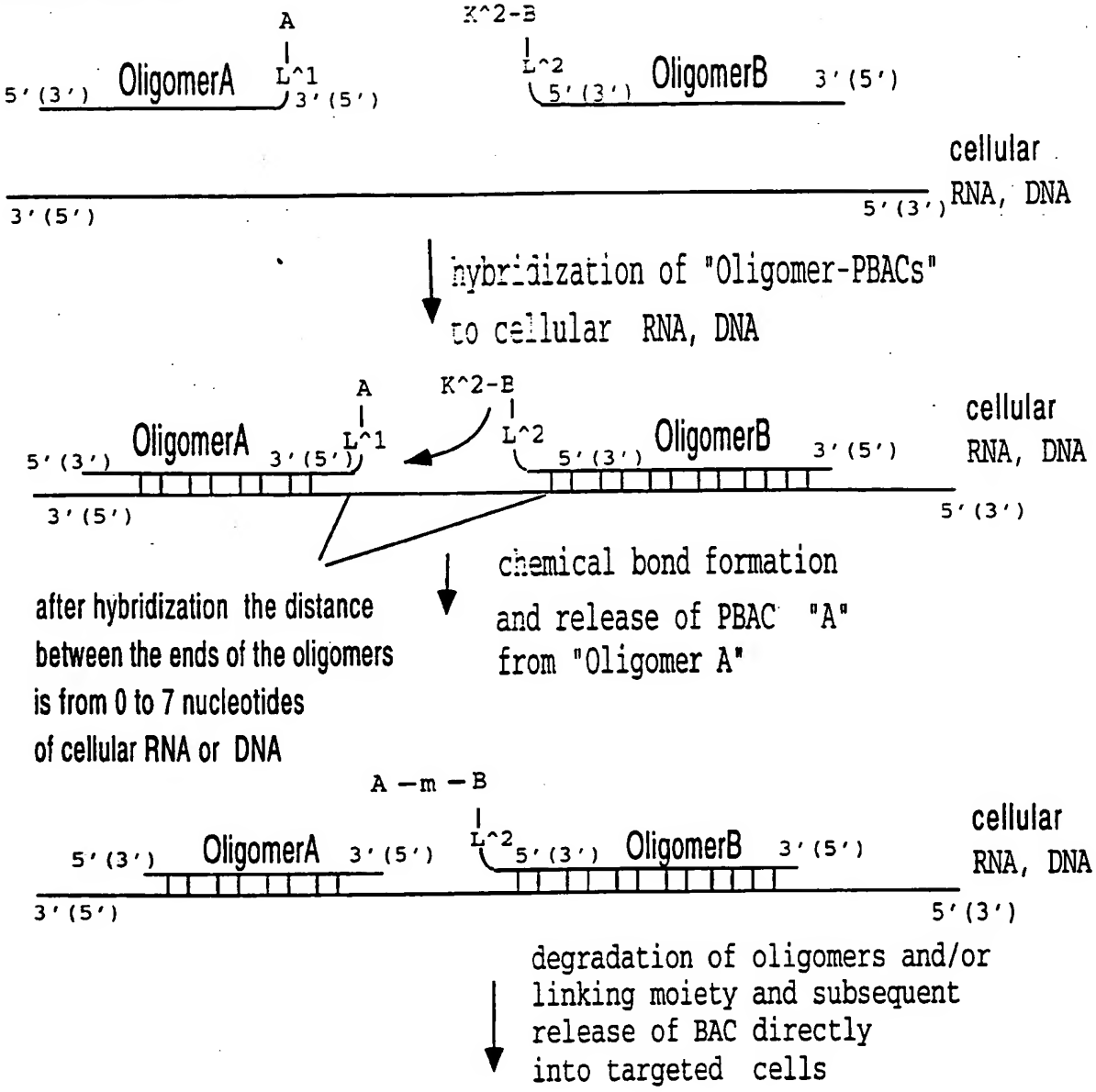
Formula 1.



"A–m–B" is the biologically active compound "T"

After hybridization of the "**Oligomer-PBACs**" "**A**" and "**B**" to cellular RNA, DNA or dsDNA, the chemically active groups K^1 and K^2 of the oligomer-**PBACs** "**A**" and "**B**" interact with each other to form the chemical moiety "m", which combines **PBACs** "A" and "B" into one active molecule of biologically active compound "T". The degradation of the oligomers and/or linking moieties L^1 and L^2 by cellular enzymes or hydrolysis leads to the release of the synthesized BAC "T" directly into the targeted cells. After hybridization of the oligomer-PBACs to cellular RNA or DNA the distance between the 3' or 5' ends of the oligomer **A** and 5' or 3' ends of the oligomer **B** is from 0 to 7 nucleotides of cellular RNA, DNA or dsDNA.

Formula 2.

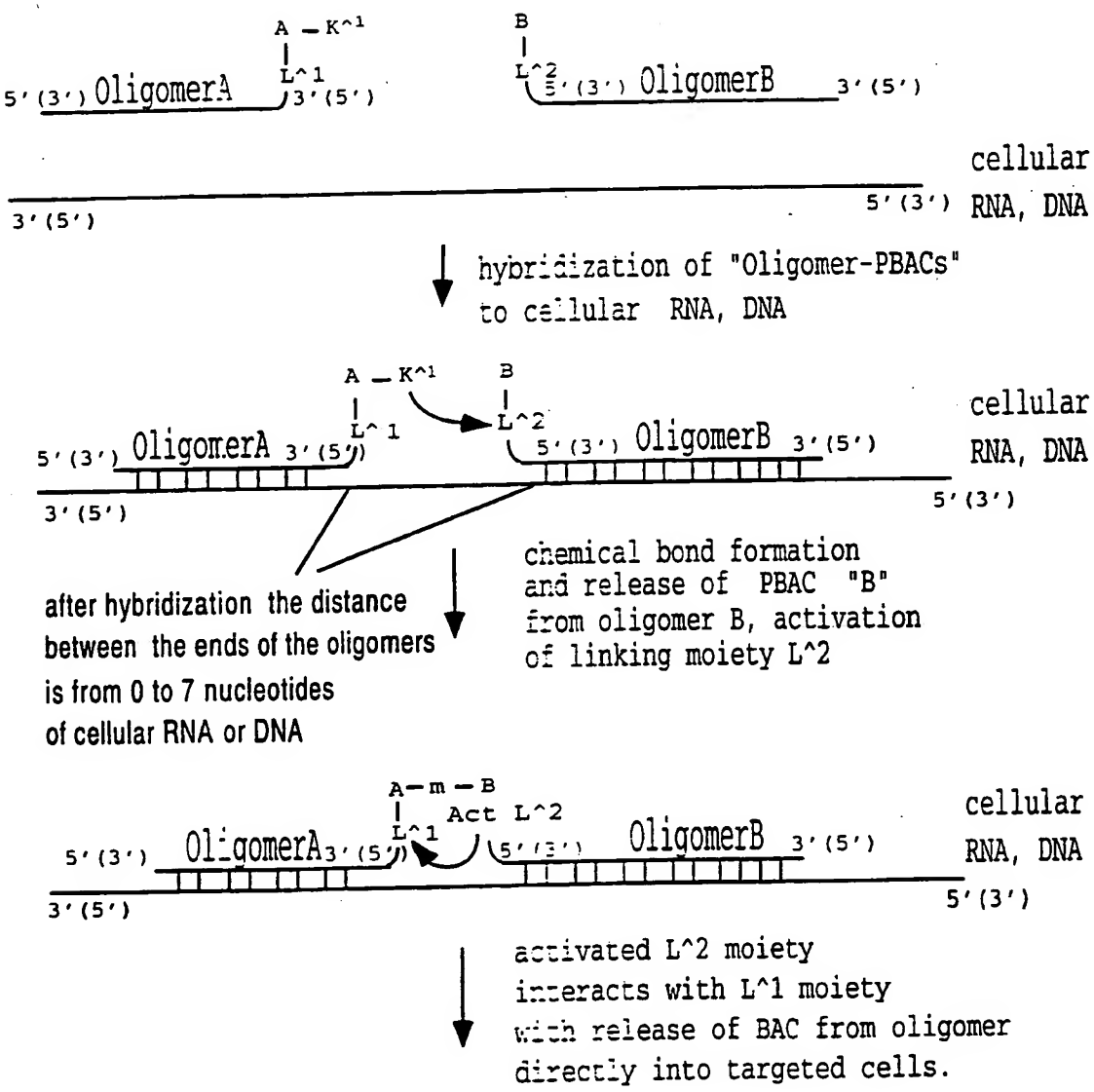


"A – m – B" is the biologically active compound "T"

After hybridization of the "oligomer-**PBAC**s" "**A**" and "**B**" to cellular **RNA**, DNA or dsDNA the chemically active group K^2 of the oligomer-**PBAC** "**B**" interacts with the linking moiety L^1 of the oligomer-**PBAC** "**A**" to combine the **PBAC**s through the chemical moiety "**m**" into one active molecule of biologically active compound "T" with the subsequent release of one **PBAC** "**B**" from the **oligomer**. The degradation of the oligomer and/or linking moieties

L^1 by cellular enzymes or hydrolysis leads to the release of synthesized BAC "T" directly into the targeted cells.

Formula 3.

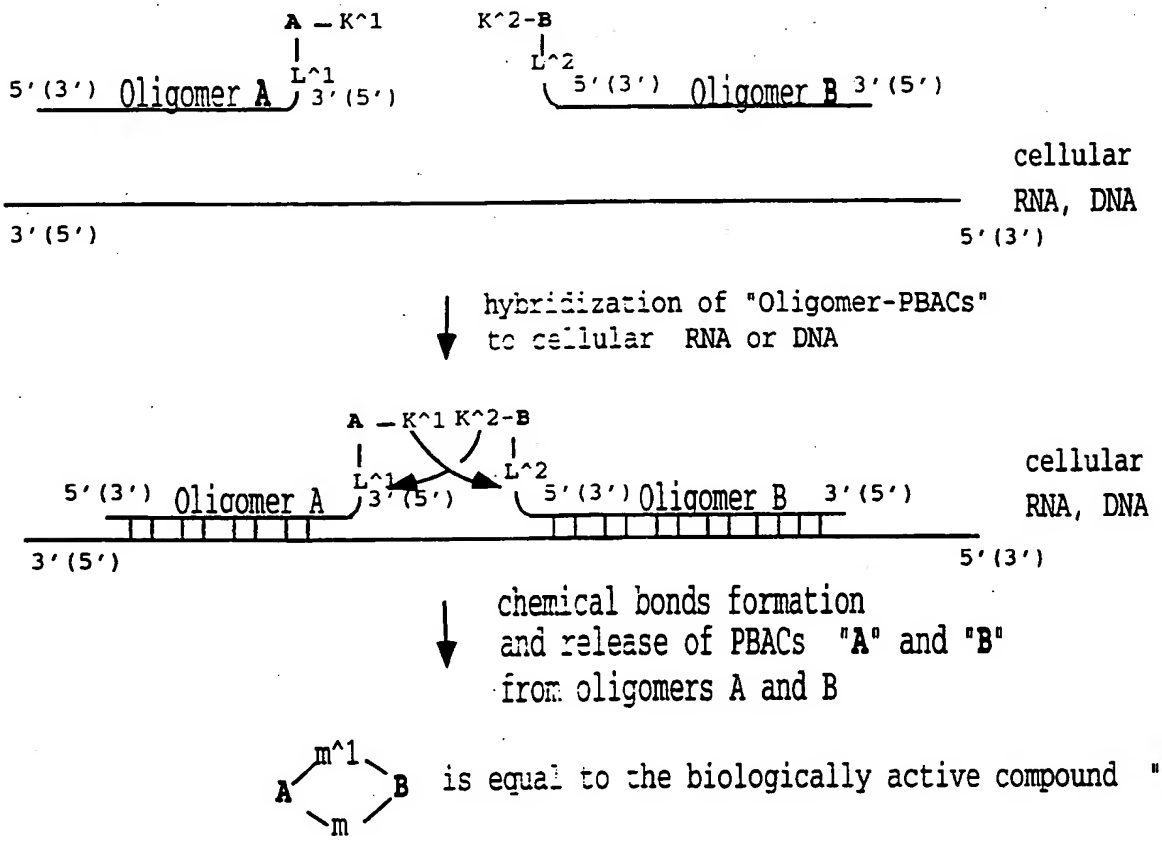


"A–m –B" is equal to the biologically active compound "T"

The chemically active group K^1 of the oligomer-**PBAC A** interacts with the linking moiety L^2 to combine the **PBACs** through the chemical moiety "m" into one active molecule of the biologically active compound "T" with the subsequnet release of one **PBAC** "**B**" from oligomer "**B**" and the activation of the chemical moiety L^2. After activation, L^2 interacts with the linking

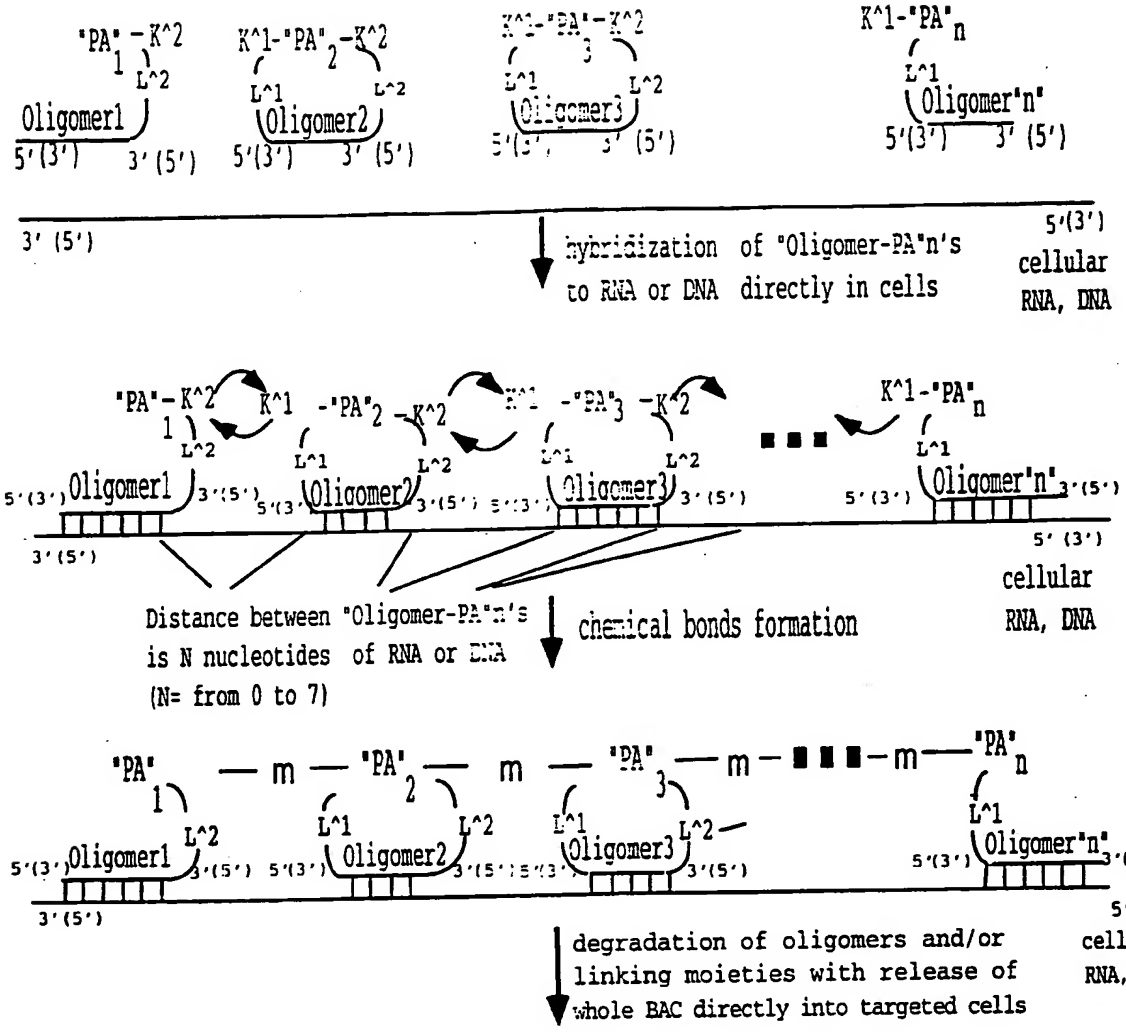
moiety L^1 to release the biological compound "T" from the oligomer directly into targeted cells.

Formula 4.



After hybridization of the "oligomer-**PBAC**s" "**A**" and "**B**" to cellular RNA, DNA or dsDNA, the chemically active group K^2 of the oligomer-**PBAC** "**B**" interacts with the linking moiety L^1 of the oligomer-**PBAC** "**A**" to combine the **PBAC**s through the chemical moiety "m". At the same time the chemically active group K^1 of the oligomer-**PBAC** "**A**" interacts with the linking moiety L^2 of the oligomer-**PBAC** "**B**" to form chemical moiety m^1. Which together with chemical moiety m combines two "Oligomer-**PBAC**s" into one active molecule of biologically active compound "T", with the release of **BAC** from the oligomer.

Formula 5.



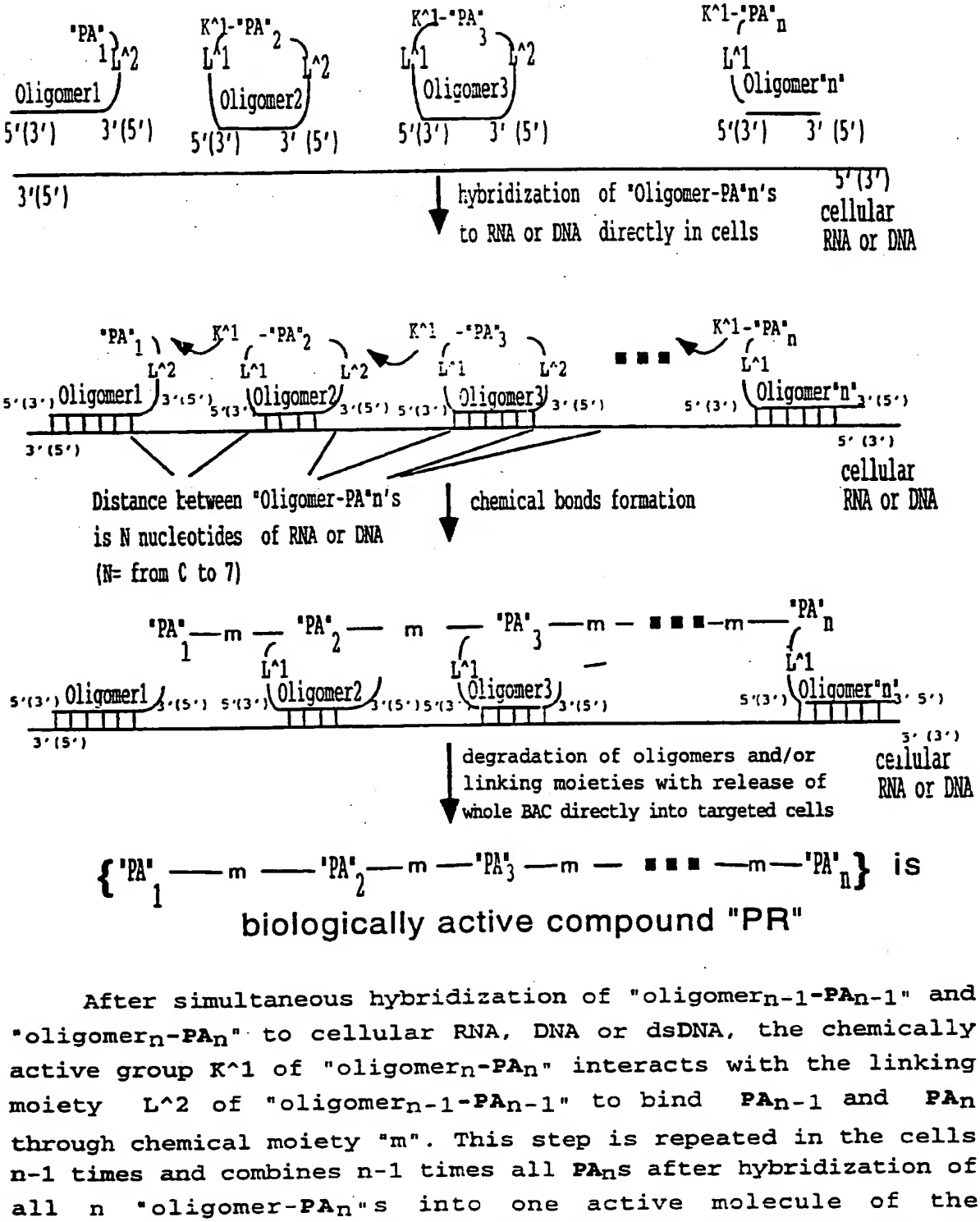
{"PA"1 — m — "PA"2 — m — "PA"3 — m — ■■■ — m — "PA"n } is

biologically active compound "PR"

After simultaneous hybridization of "**Oligomer$_{n-1}$-PA$_{n-1}$**" and "**Oligomer$_n$-PA$_n$**" to cellular RNA or DNA, the chemically active groups K^1 and K^2 interact with each other to form the chemical moiety "m" between "**Oligomer$_{n-1}$-PA$_{n-1}$**" and "**Oligomer$_n$-PA$_n$**" correspondingly; This step is repeated in the cells n-1 times and combines n-1 times all "**PA$_n$**"s into one active molecule of the biologically active compound "PR" which consists of n **PA$_n$** so that compound {"**PA**"1-m-"**PA**"2-m-"**PA**"3-m-"**PA**"4-m-...-m-"**PA$_n$**-3"-m-"**PA$_n$**-2"-m-"**PA$_n$**-1"-m-"**PA$_n$**"} is biologically active compound "PR". The degradation of the oligomers and/or linking moieties L^1 and L^2 leads to the release of the synthesized BAC "PR"

directly into targeted cells of living organism. Here, n is selected from 2 to 2000;

Formula 6.

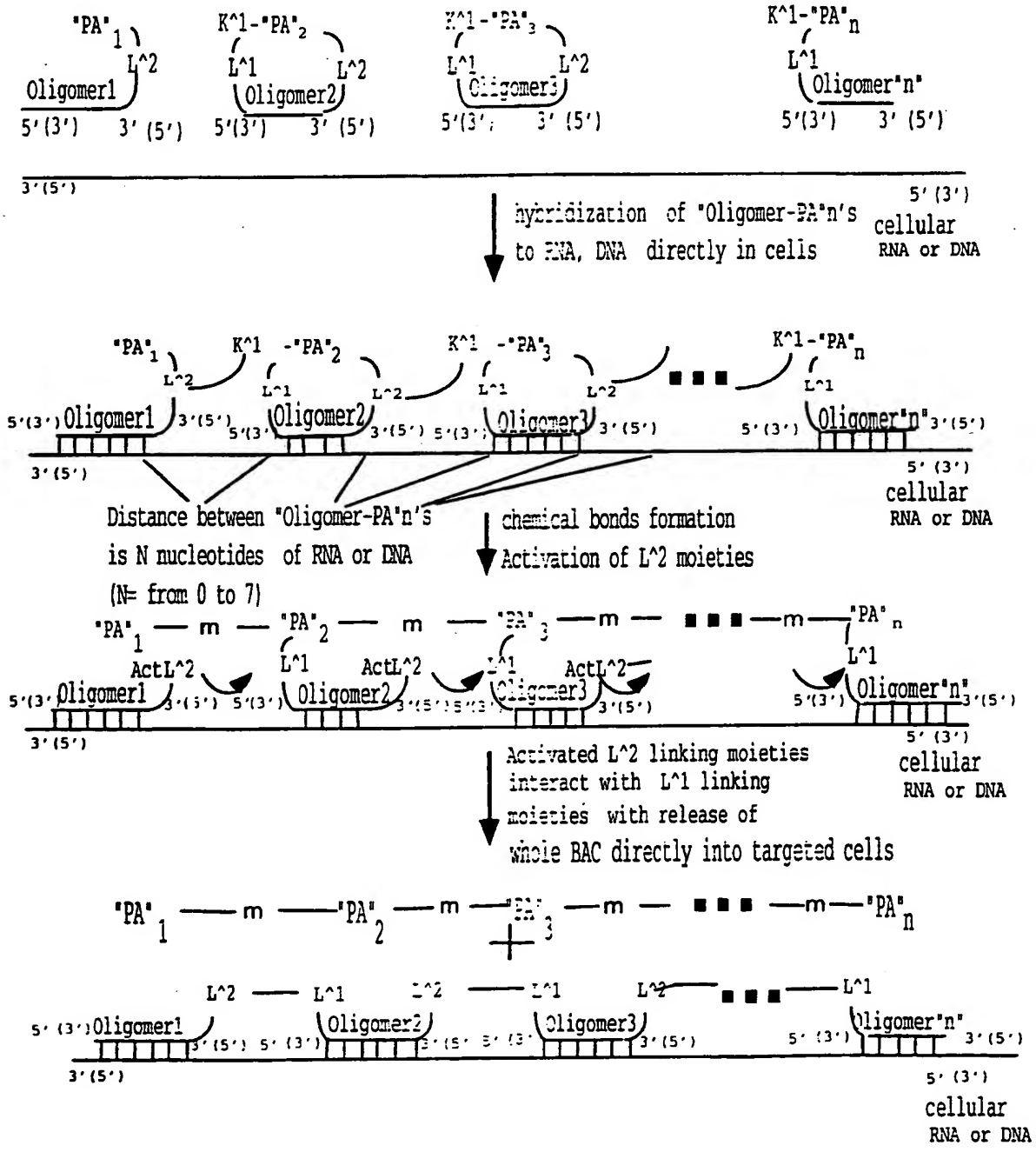


$$\{"PA"_1 - m - "PA"_2 - m - "PA"_3 - m - \blacksquare\blacksquare\blacksquare - m - "PA"_n\} \text{ is biologically active compound "PR"}$$

After simultaneous hybridization of "oligomer$_{n-1}$-**PA**$_{n-1}$" and "oligomer$_n$-**PA**$_n$" to cellular RNA, DNA or dsDNA, the chemically active group K^1 of "oligomer$_n$-**PA**$_n$" interacts with the linking moiety L^2 of "oligomer$_{n-1}$-**PA**$_{n-1}$" to bind **PA**$_{n-1}$ and **PA**$_n$ through chemical moiety "m". This step is repeated in the cells n-1 times and combines n-1 times all **PA**$_n$s after hybridization of all n "oligomer-**PA**$_n$"s into one active molecule of the biologically active compound "PR", which consists of n **PA**s so

that compound {**PA**$_1$-m-**PA**$_2$-m-**PA**$_3$-m-**PA**$_4$-m-...-m-**PA**$_{n-3}$-m-**PA**$_{n-2}$-m-**PA**$_{n-1}$-m-**PA**$_n$} is equal to the biologically active compound PR. The degradation of the oligomers and/or linking moieties L^1 by cellular enzymes or hydrolysis leads to the release of the synthesized BAC PR directly into targeted cells of living organism, here n is selected from 1 to 2000;

Formula 7.



10

After simultaneous hybridization of "**Oligomer$_{n-1}$-PA$_{n-1}$**" and "**oligomer$_n$-PA$_n$**" to cellular RNA, DNA or dsDNA, the chemically active group K^1 of "**oligomer$_{n-1}$-PA$_{n-1}$**" interacts with the linking moiety L^2 of "**oligomer$_n$-PA$_n$**" to bind **PA$_{n-1}$** and **PA$_n$** through chemical moiety "m". After interaction of K^1 with L^2, L^2 is chemically activated so that it can interact with linking moiety L^1 of the oligomer-**PA$_{n-1}$**, thus destroying the binding of the oligomer$_{n-1}$ to **PA$_{n-1}$**. This process is repeated n-1 times, so that only whole BAC "PR" comprising from n **PA$_n$**s (**PA$_1$**-m-**PA$_2$**-m-**PA$_3$**-m-**PA$_4$**-m-...-m-**PA$_{n-3}$**-m-**PA$_{n-2}$**-m-**PA$_{n-1}$**-m-**PA$_n$**) is released directly into the targeted cells of living organisms, here n is selected from 2 to 2000.

The chemical moieties in the Formulas 1,2,3,4,5,6 and 7 are as follows:

m is selected independently from: -S-S-, -N(H)C(O)-, -C(O)N(H)-, -C(S)-O-, -C(S)-S-, -O-, -N=N-, -C(S)-, -C(O)-O-, -NH-, -S-;

K^1 is selected independently from: -NH(2), dbdNH, -OH, -SH, -F, -Cl, -Br, -I, -R^1-C(X)-X^1-R^2;

K^2 is selected independently from: - NH(2), -dbd-NH, -OH, SH, -R^1-C(X)-X^1-R^2, -F, -Cl, -Br, -I;

L^1 is independently: chemical bond, -R^1-, -R^1-O-S-R^2-, -R^1-S-O-R^2-, -R^1-S-S-R^2-, -R^1-S-N(H)-R^2-, -R^1-N(H)-S-R^2-, -R^1-O-N(H)-R^2-, -R^1-N(H)-O-R^2-, -R^1-C(X)-X^1-R^2-;

L^2 is independently: chemical bond, -R^1-, -R^1-O-S-R^2-, -R^1-S-O-R^2-, -R^1-S-S-R^2-, -R^1-S-N(H)-R^2-, -R^1-N(H)-S-R^2-, -R^1-O-N(H)-R^2-, -R^1-N(H)-O-R^2-, -R^1-C(X)-X^1-R^2-, -R^1-X-C(X)-X-C(X)-X-R^2-;

R^1 is independently: chemical bond, alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl, cycloheteroaryl, carbocyclic, heterocyclic ring, X^1-P(X)(X)-X^1, -S(O)-, -S(O)(O)-, -X^1-S(X)(X)-X^1-, -C(O)-, -N(H)-, -N=N-, -X^1-P(X)(X)-X^1-, -X^1-P(X)(X)-X^1-

P(X)(X)-X^1, -X^1-P(X)(X)-X^1-P(X)(X)-X^1-P(X)(X)-X^1, -C(S)-, any suitable linking group;

R^2 is independently chemical bond, alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl, cycloheteroaryl, carbocyclic, heterocyclic ring, X^1-P(X)(X)-X^1, -S(O)-, -S(O)(O)-, -X^1-S(X)(X)-X^1-, -C(O)-, -N(H)-, -N=N-, -X^1-P(X)(X)-X^1-, -X^1-P(X)(X)-X^1-P(X)(X)-X^1, -X^1-P(X)(X)-X^1-P(X)(X)-X^1-P(X)(X)-X^1, -C(S)-, any suitable linking group;

X is independently S, O, NH, Se, alkyl, alkenyl, alkynyl;
X^1 is independently S, O, NH, Se, alkyl, alkenyl, alkynyl.

In Formulas 1,2,3,4,5,6 and 7 the linking moieties L^1 and L^2 are bound to the first and/or last mononucleomers of the oligomers at their sugar or phosphate moiety, or directly to base, or to sugar moiety analogues, or to phosphate moiety analogues, or to base analogues.

All the described schemes demonstrate that BACs can not be synthesized in non-targeted cells because the molar concentration of the chemically active groups is too low, and without hybridization of the oligomer-**PBACs** to the template, specific reactions can not occur. After hybridization of the oligomer-**PBACs** to a specific template, the concentration of the chemically active groups is sufficient for the chemical reaction between the chemical groups of **PBACs** to occur. The reaction leads to chemical bond formation between **PBACs** and subsequent formation of a whole BAC. The degradation of the oligomers and/or linking moieties of the oligomers with **PBACs** leads to the release of BACs directly into targeted cells. To synthesise biologically active polymers such as proteins and RNAs of determined structure directly into cells more than two **PBACs** can be used. PBACs for synthesis of proteins or RNAs are designated as $\mathbf{PA_n}$. $\mathbf{Pa_n}$ are peptides or oligoribonucleotides. The mechanisms of the interaction of such **PBACs** are the same as in the synthesis of small biologically active compounds. The difference is that the **PBACs** (with the exception of the first and last PBACs) are bound simultaneously

to the 5' and 3' ends of the oligomers so that the direction of synthesis of the biologically active protein or RNA can be determined.

Possible functions of BACs synthesized by proposed methods are: 1) Killing of cells, 2) Stimulation of the metabolism of cells 3) Blocking of important ion channels such as Na^+, K^+, Ca^{++} and other ion channels, in order to inhibit signal transmissions. BACs can be proteins, peptides, alkaloids and synthetic organic compounds. They can be cleaved into two or more precursors called **PBACs**. After interaction between the chemical groups of **PBACs**, whole BAC is formed through the moiety "m".

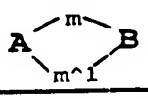
a) In Formula 1,2,3 and 4 **PBACs** are designated as "**A**" and "**B**"

A-"m"-**B** is equal to a whole BAC "**T**"

"m" is selected independently from -S-S-, -O-, -NH-C(O)-, -C(O)-NH-, -C(O)-, -NH-, dbdN-, -C(O)O-, -C(O)S-, -S-, -C(S)S-, -C(S)O, -N=N-.

A-O-**B**	is equal to a whole BAC	"**T**"
A-NH-C(O)-**B**	is equal to a whole BAC	"**T**"
A-C(O)-NH-**B**	is equal to a whole BAC	"**T**"
A-C(O)-**B**	is equal to a whole BAC	"**T**"
A-NH-**B**	is equal to a whole BAC	"**T**"
A-dbdN--**B**	is equal to a whole BAC	"**T**"
A-C(O)O-**B**	is equal to a whole BAC	"**T**"
A-C(O)S-**B**	is equal to a whole BAC	"**T**"
A-C(S)S-**B**	is equal to a whole BAC	"**T**"
A-S-S-**B**	is equal to a whole BAC	"**T**"
A-C(S)O-**B**	is equal to a whole BAC	"**T**"
A-N=N-**B**	is equal to a whole BAC	"**T**"

b) A biologically active compound can be formed through the moieties "m" and "m^1". "m" and "m^1" are selected independently from: -S-S-, -O-, -NH-C(O)-, -C(O)-NH-, -C(O)-, -NH-, dbdN-, -C(O)O-, -C(O)S-, -S-, -C(S)S-, -C(S)O, -N=N-, so that



is equal to biologically active compound "T"

This kind of interaction is represented in figure 4.

c) In Formulas 5, 6 and 7, precursors of BACs (**PBACs**) are designated as "**PA**n", where n is selected from 2 to 2000. "**PA**" are peptides or oligoribonucleotides consisting of from 2 to 100 amino acids or ribonucleotides correspondingly. n is the ordinal number of PA in a series of PAs and designates the sequence of binding of PAs to each other.

{"**PA**1"-m-"**PA**2"-m-"**PA**3"-m-..-m-"**PA**n-3"-m-"**PA**n-2"-m-"**PA**n-1"-m-"**PA**n"} is equal to BAC "PR". BACs "PR" in this case are proteins or RNAs. Proteins can be cellular proteins, enzymes, transcription factors, ligands, signalling proteins, transmembrane proteins, cytolitical toxins, cytoplasmic and nuclear proteins and the like. RNAs are selected from mRNA, rsRNA and the like.

Brief description of drawings.

Fig.1 Synthesis of the toxin daphnoretin.

Toxin Daphnoretin is cleaved into two precursors. After simultaneous hybridization to cellular RNA of the oligomers bound to the daphnoretin's precursors, the chemically active hydroxyl group of daphnoretin's precursor "A" interacts with the chemically active Cl group of precursor "B" to form a chemical bond between two daphnoretin precursors. The degradation of the linking moieties and/or oligomers leads to the release of the biologically active molecule directly into targeted cells.

Fig.2 Synthesis of the neurotoxin peptide,

Neurotoxin is cleaved into two shorter, biologically inactive peptides. After hybridization to cellular RNA or DNA, the chemically active NH_2 group of peptide "**A**" interacts with the linking moiety -C(O)-O-L^2, forming a peptidyl bond. After the peptidyl bonds formation, the chemically active group -SH of peptide "**B**" interacts with the linking moiety L^1-S-S- which binds peptide "**A**" with oligomer "**A**". After this interaction, an -S-S- bound between the two cysteins is formed and the biologically active neurotoxin is released into targeted cells. Amino acids are designated as italicised letters in one letter code.

Fig.3 The synthesis of the toxin tulopsoid A.

Toxin tulopsoid A is cleaved into two precursors. After simultaneous hybridization to cellular RNA of the oligomers bound to the tulopsoid A precursors chemically active hydroxyl group of the oligomer-**PBAC** "A" interacts with the $-CH_2-S-C(O)-$ linking moiety to form a chemical bond with tulopsoid's precursor "B", releasing precursor "B" from oligomer 2. The activated $-CH_2-SH$ moiety interacts with the linking moiety -S-O-, releasing the whole tulopsoid A from oligomer 1.

Fig.4 Synthesis of the toxin amanitin.

Toxin-amanitin is a strong inhibitor of transcription. It can be cleaved into two inactive precursors, which can be used to synthesise the whole molecule of amanitin. After hybridization of all oligomers bound with the amanitin's precursors to cellular RNA or DNA, free amino group of amanitin's precursor "A" can interact with the carboxyl group -C(O)-S-L^2 to form a peptidyl bond and to release amanitin's precursor "B" from oligomer 2. The linking moiety of amanitin's precursor "A" to the oligomer 1 is semistabile. The release of precursor "A" from the oligomer 1 is performed due to action of the activated -SH group on the linking moiety -C(O)-O-S-L^1. Oligomers 3 and 4 bound with the amanitin's precursors "**A**" and "**B**" are hybridized on the same molecule of RNA or DNA. The amino group of amanitin's precursor "**B**" interacts with the carboxyl group -C(O)-S-L^1 to form a peptidyl bond, releasing amanitin's precursor "**A**" from the oligomer 3. The linking moiety of amanitin's precursor "B" to the oligomer 4 is semistabile. The release of precursor "B" from the oligomer 4 is performed due to action of the activated -SH group on the linking moiety -C(O)-O-S-L^2.

Fig.5 Synthesis of the toxin D-actinomicin.

Toxin D-actinomicin is cleaved into two precursors. After simultaneous hybridization of two oligomer-**PBAC**s to cellular RNA or DNA chemically active amino and halogen groups of precursor "A" interact with the chemically active halogen and hydroxyl groups of D-actinomicin's precursor "B" respectively to form two chemical bonds between the precursors.

Fig.6 Synthesis of the toxin ochratoxin A.

Toxin ochratoxin A is cleaved into two precursors, which are bound to oligomers. After simultaneous hybridization of the oligomer-**PBAC**s to cellular RNA or DNA, the chemically active amino group of precursor "B" interacts with the moiety C(O)-O-

which links precursor "A" with oligomer A, to form a chemical bond between the two ochratoxin precursors. After oligomer or linking moiety degradation in the cells the whole biologically active molecule of Ochratoxin A is released into the targeted cells.

Fig.7 Synthesis of the toxin ergotamin

Toxin ergotamin is cleaved into two precursors, which are bound to oligomers. After simultaneous hybridization of the oligomer-**PBAC**s to cellular RNA or DNA, the chemically active amino group of precursor "B" interacts with the moiety C(O)-O- which binds precursor "A" with oligomer "A", to form a chemical bond between the two ergotamin precursors. After degradation of the oligomers, RNA, or DNA in the cells, the whole biologically active molecule of ergotamin is released into the targeted cells.

Fig 8. Synthesis of proteins.

The synthesis of a biologically active protein of n peptides.

Peptides are bound to oligomers simultaneously at their amino and carboxy ends, with the exception of the first peptide, which is bound to the oligomer at its carboxy end, and the last peptide, which is bound to the oligomer at its amino terminal. Two oligomers bound to peptides (**oligomer-PA**s) are hybridized simultaneously to specific RNA or DNA molecules, the distance from each other between 0 and 10 nucleotides of cellular RNA or DNA. After hybridization, the amino group of the oligomer-PA_n interacts with the -L^2-S-C(O)- linking moiety to form a peptidyl bond between peptide "n-1" and peptide "n". The $peptide_{n-1}$ is released from the $oligomer_{n-1}$ at its carboxy terminal. The activated -L^2-SH group interacts then with the linking moieties -O-S-L^1 and -O-NH-L^1 which bind $peptides_n$ at their amino terminal with $oligomers_n$. After hybridization of all n oligomer-**PA**s the process is repeated n-1 times to bind all n peptides into one biologically active protein. Linking of the peptides at the amino terminal with oligomers is performed by amino acids which have hydroxyl group such as serine, threonine and tyrosine.

Fig 9. Synthesis of proteins.

The same process is shown as in figure 8, but this time the peptides are bound at their amino terminal to oligomers through aminoacids with amino and mercapto groups, for example cysteine, arginine, asparagine, glutamine and lysine. The activated -L^2-SH

group can interact with the linking groups such as -S-S-L^1, -S-NH-L^1 to form -L^2-S-S-L^1-, -L^2-S-NH-L^1 moieties and to release peptides from oligomers.

Fig 10. Synthesis of RNA

In this figure "**PA**$_n$" are oligoribonucleotides comprising from 3 to 300 nucleotides.

n in "**PA**$_n$" means the ordinal number in a series of oligoribonucleotides used in the synthesis of whole RNA, where n is selected from 2 to 1000.

PA$_1$ couples with **PA**$_2$ through the chemical moiety -O-, then in turn **PA**$_1$-m-**PA**$_2$ couples with **PA**$_3$ through chemical moiety -O-, then **PA**$_1$-m-**PA**$_2$-m-**PA**$_3$ couples with **PA**$_4$ through chemical moiety -O- and so on until the last "n"th oligoribonucleotide is bound, forming the whole biologically active RNA.

The chemical moieties in figures from 1 to 10 are as follows:

m is selected independently from: -S-S-, -N(H)C(O)-, -C(O)N(H)-, -C(S)-O-, -C(S)-S-, -O-, -N=N-, -C(S)-, -C(O)-O-, -NH-, -S-;

K^1 is selected independently from: -NH(2), dbdNH, -OH, -SH, -F, -Cl, -Br, -I, -R^1-C(X)-X^1-R^2;

K^2 is selected independently from: - NH(2), - dbd-NH, -OH, -SH, -R^1-C(X)-X^1-R^2, -F, -Cl, -Br, -I;

L^1 is independently: chemical bond, -R^1-, -R^1-O-S-R^2-, -R^1-S-O-R^2-, -R^1-S-S-R^2-, -R^1-S-N(H)-R^2-, -R^1-N(H)-S-R^2-, -R^1-O-N(H)-R^2-, -R^1-N(H)-O-R^2-, -R^1-C(X)-X^1-R^2-;

L^2 is independently: chemical bond, -R^1-, -R^1-O-S-R^2-, -R^1-S-O-R^2-, -R^1-S-S-R^2-, -R^1-S-N(H)-R^2-, -R^1-N(H)-S-R^2-, -R^1-O-N(H)-R^2-, -R^1-N(H)-O-R^2-, -R^1-C(X)-X^1-R^2-, -R^1-X-C(X)-X-C(X)-X-R^2-;

R^1 is independently: chemical bond, alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl, cycloheteroaryl, carbocyclic, heterocyclic ring, X^1-P(X)(X)-X^1, -S(O)-, -S(O)(O)-, -X^1-S(X)(X)-X^1-, -

C(O)-, -N(H)-, -N=N-, -X^1-P(X)(X)-X^1-, -X^1-P(X)(X)-X^1-P(X)(X)-X^1, -X^1-P(X)(X)-X^1-P(X)(X)-X^1-P(X)(X)-X^1, -C(S)-, any suitable linking group;

R^2 is independently chemical bond, alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl, cycloheteroaryl, carbocyclic, heterocyclic ring, X^1-P(X)(X)-X^1, -S(O)-, -S(O)(O)-, -X^1-S(X)(X)-X^1-, -C(O)-, -N(H)-, -N=N-, -X^1-P(X)(X)-X^1-, -X^1-P(X)(X)-X^1-P(X)(X)-X^1, -X^1-P(X)(X)-X^1-P(X)(X)-X^1-P(X)(X)-X^1, -C(S)-, any suitable linking group;

X is independently S, O, NH, Se, alkyl, alkenyl, alkynyl;
X^1 is independently S, O, NH, Se, alkyl, alkenyl, alkynyl.

Best mode for carrying out the invention.

The synthesis of different toxins and alkaloids directly into targeted cells.

Example 1. The synthesis of the toxin alpha amanitin.

The amanitin is a toxin present in mushrooms. It acts as a very strong inhibitor of transcription in eucaryotic cells, and is therefore very strong toxin.

The synthesis of alpha-amanitin is represented in Fig.4 The structure of the toxin is a cyclic peptide with modified amino acids. The molecule of alpha-amanitin can be cleaved into two inactive precursors, which are bound to 4 oligomers through linking moieties L^1 and L^2, designated in Figure 4. After hybridization of all oligomers to the same molecule of RNA the synthesis of toxin amanitin is occurred.

Example 2. The synthesis of biologically active peptides.

The synthesis of BACs consisting of amino acids makes possible the synthesis of practically any peptide. These peptides can be involved in a wide variety of processes. The specific synthesis will occur only in the cells where the specific sequences are represented.

The synthesis of peptides such as endorphins or toxins which block Na, K, Ca channels can be performed directly on specific RNA or DNA sequences. These peptides can act as agents

stimulating cells of the nervous system, or as analgesic agents. To date, the number of known biologically active peptides is enormous. The peptides can be synthesized from natural amino acids as well as from synthetic amino acids of D or L conformations.

The synthesis of neurotoxin is represented in Fig.2.

Example 3. The synthesis of the toxin tulopsoid A.

Toxin tulopsoid A is an alkaloid and is a strong cytolitical toxin. Toxin tulopsoid A is cleaved into two precursors. The chemically active hydroxyl group of precursor "A" can interact after hybridization with the $-CH_2-S-C(O)-$ moiety to form a chemical bond with tulopsoid's precursor "B", with the release of precursor "B" from the oligomer. The activated $-CH_2-SH$ moiety interacts with the linking moiety -S-O-, releasing the whole tulopsoid from oligomer (Fig. 3.).

Example 4. The synthesis of the toxin daphnoretin.

Toxin daphnoretin is an alkaloid and is a strong cytolitical toxin.

Toxin Daphnoretin is cleaved into two precursors. After simultaneous hybridization of the oligomers coupled to the daphnoretin's precursors the chemically active hydroxyl group of daphnoretin's precursor "A" interacts with the chemically active Cl group of precursor "B" to form chemically bond between daphnoretin's precursors. The degradation of the oligomers or linking groups leads to the release of the biologically active molecule directly into targeted cells (Fig.4).

Example 5. The synthesis of the toxin D-actinomicin.

Toxin D-actinomicin is an alkaloid and is a strong cytolitical toxin.

Toxin D-actinomicin is cleaved into two precursors. After hybridization of two oligomers to cellular RNA or DNA, the chemically active groups amino and halogen of precursor "A" interact with the chemically active groups halogen and hydroxyl respectively of D-actinomicin's precursor "B" to form two chemical bonds between the precursors (Fig 5.).

Example 6. The synthesis of the toxin ochratoxin A.

Toxin ochratoxin A is an alkaloid and is a strong cytolitical toxin.

Toxin ochratoxin A is cleaved into two precursors bound to oligomers. After hybridization of the oligomers to cellular RNA

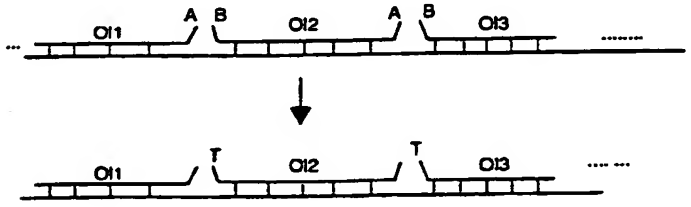
or DNA, the chemically active amino group of the precursor "B" interacts with the moiety -O-C(O) of precursor "A" to form a chemical bond between the two ochratoxin precursors. After the degradation of the oligomers or linking moieties in the cells, whole, biologically active molecules of Ochratoxin A will be released into targeted cells (Fig. 6.).

Example 7. The synthesis of the toxin ergotamin

Toxin ergotamin is an alkaloid and is a strong cytolitical toxin.

Toxin ergotamin is cleaved into two precursors which are bound to oligomers. After hybridization of the oligomers to cellular RNA or DNA, the chemically active amino group of precursor "B" interacts with moiety -O-C(O) of precursor "A" to form a chemical bond between the two ergotamin precursors. After degradation of the oligomers or linking moieties in the cells, whole, biologically active molecules of ergotamin will be released into the targeted cells.

By using more than two oligonucleotides bound at their 5',3' ends to precursors of biologically active compounds, higher concentration level of the biologically active substances can be achieved into targeted cells.



O11, O12, O13 are oligomers 1,2,3 which at their 3' and 5' ends are bound to precursors of biologically active substances.

Such linking can also prevent oligonucleotides from exonuclease degradation and stabilise their activity in cells. In any case, the products of the degradation of the peptides and oligonucleotides formed from natural amino acids and nucleotides are not toxic, and can be used by cells without elimination from the organism or toxic effects on other healthy cells.

All the toxins described can be used for the synthesis of toxins in cells infected by viruses, using the hybridization of the oligomers to double stranded DNA. In USA patent 5,571,937 the homopurine sequences of HIV 1 were found.

One such sequence is 5'-GAAGGAATAGAAGAAGAAGGTGGAGAGAGAGA-3' (seq ID NO 43 USA patent 5,571,937). Using two oligomers: (A-5'-GAAGGAATAGAAGAAG-3') and (B-5'-AAGAAGGTGGAGAGAGAGA-3') bound through linking moieties L^1 and L^2 to PBACs, synthesis of the corresponding BACs directly in human cells infected by HIV1 can be achieved. The toxin will be synthesized only in those cells infected by HIV1. Other healthy cells will be not killed by synthesized toxin.

The synthesis of proteins

The synthesis of protein can be performed according to the scheme designated in Formulas 5, 6 and 7 and in Figs.8,9.

Relatively small molecules can be used to synthesise the whole active proteins in any tissue of a living organism. These small molecules can easily penetrate the blood brain barrier, or enter other tissues. The degradation products of such compounds can be used as nutrients for other cells. They are also not toxic to other cells where specific RNAs are not present, in the case where oligomers are oligoribo(deoxy)nucleotides. The synthesis of whole proteins of 50 kDa can be performed on one template 300-500 nucleotides in length using oligomers of the length 10-50 nucleomonomers bound to peptides consisting of 2-30 amino acids. Only 10-20 such **PBACs** are necessary to synthesise a protein of molecular weight 50 kDa. Theoretically, it is possible to synthesise the proteins of any molecular mass. The number of oligomer-**PAs** can vary from 1 to 1000, but the efficiency of synthesis of large proteins is very low and depends on the velocity of the reaction and the degradation of the oligomer-**PAs** in the living cells.

By this method, synthesized proteins can be modified later in the cells by cellular enzymes to achieve the biologically active form of the protein.

The method allows the synthesis of specific proteins only in those cells in which the proteins are needed. Any type of proteins can be synthesized by this method. These proteins can be involved in cellular metabolism, transcription regulation,

enzymatic reactions, translation regulation, cells division or apoptosis.

The mechanism allows the synthesis of any protein directly into targeted cells. The synthesized proteins could inhibit a cell's growth or division, or could stimulate division and metabolism of cells where specific RNAs are expressed. By the method described, it is possible to synthesise not only one protein, but also many different proteins in the selected cells. These proteins could change even the differentiation of the targeted cells. The targeted cells can be somatic cells of living organisms, tumour cells, cells of different tissues, bacterial cells or cells infected by viruses.

Example 8 Synthesis of the tumour suppresser p53.

The synthesis is performed according to Formula 6. In the example below, the peptides from PA_2 to PA_{14} are bound at their NH_2 end to the linking moiety L^2 through the OH group of amino acids serine or threonine. The linking moiety L^2 is bound to the phosphate or sugar moiety of the nucleotides localised at the 5' end of the corresponding oligomers. The amino acids at the COOH ends of the peptides are bound to the oligomer through acyl moieties (L^1) bound to the 3' OH group of sugar moiety of the nucleotide localised at 3' end. After hybridization to specific cellular RNA, the NH_2 group of the $oligomer_n$-PA_n interacts with the linking acyl group of the $oligomer_{n-1}$-PA_{n-1} to form a peptidyl bond between two oligomer-PAs. The whole P53 protein can be synthesized using only 14 oligomer-PAs and a 250 nucleotide long region of RNA for hybridization to the oligomer-PAs.

PA_1, PA_2, PA_3, PA_4, PA_5, PA_6, PA_7, PA_8, PA_9, PA_{10}, PA_{11}, PA_{12}, PA_{13} and PA_{14} are the peptides which are bound to the oligomers. The sequences of the peptides are represented below.

PA_1 -*MEEPQSDPSV EPPLSQETFS DLWKLLPENN VL*
PA_2 -*SPLPSQAM DDLMLSPDDI EQWF*
PA_3 -*TEDPGPDEAP RMPEAAPRVA PAPAAP*
PA_4 -*TPAAPAPAPS WPLSSSVPSQ KTYQG*
PA_5 -*SYGFRLGFLHS GTAKSVTCTY*
PA_6 -*SPAL NKMFCQLAKT CPVQLWVDSTPPPG*
PA_7- *TRVRAM AIYKQSQHMT EVVRRCPHHE*
PA_8 - *TCSDSDGLAP PQHLIRVEGN LRVEYLDDRN*

PA_9 - ***TFRHSVVVPY EPPEVGSDCT TIHYNYMCNS***

PA_{10} - ***SCMGGMNRRP ILTIITLEDS SGNLLGRN***

PA_{11} -***SFEVRVCACPGR DRRTEEENLR KKGEPHHELPPG***

PA_{12} -***STKRALPN NTSSSPQPKK KPLDGEYF***

PA_{13} -***TLQIRGRERFEM FRELNEALEL KDAQAGKEPGG***

PA_{14} -***SRAHSSHLK SKKGQSTSRH KKLMFKTEGP DSD***

Amino acids are designated in bold/italicised one letter code.

A - alanine, ***R*** - arginine, ***N*** - asparagine, ***D*** - aspartic acid, ***C***- cysteine, ***Q*** -glutamine, ***E*** - glutamic acids, ***G*** - glycine, ***H*** - histidine, ***I*** - isoleucine, ***L*** -leucine, ***K*** - lysine, ***M*** - methionine, ***F*** - phenylalanine, ***P***- proline, ***S*** - serine, ***T*** - threonine, ***W***- tryptophan, ***Y*** - tyrosine, ***V*** - valine.

The tyrosine in **PA**$_7$ can be chemically phosphorylated. In this way an already active form of the protein can be synthesized directly in the cells. It is possible to include any modification at any amino acid of the **PAs**.

oligomer 1 5'-cccaatccctcttgcaactga-3'

oligomer 2 5'- attctactacaagtctgccctt-3'

oligomer 3 5'-ttgtgaccggctccactg-3'

oligomer 4 5'-taccttggtacttctctaa-3'

oligomer 5 5'-atgccatattagcccatcaga-3'

oligomer 6 5'-ccaagcattctgtccctccttt-3'

oligomer 7 5'-tccggtccggagcacca-3'

oligomer 8 5'-gccatgacctgtatgttaca-3'

oligomer 9 5'-ggtgtgggaaagttagcggg-3'

oligomer 10 5'-gcgaattccaaatgattttaa-3'

oligomer 11 5'-aatgtgaacatgaataa-3'

oligomer 12 5'-agagtgggatacagcatctata-3'

oligomer 13 5'-acaaaaccattccactctgatt-3'

oligomer 14 5'-ttggaaaaactgtgaaaaa-3'

All oligomers herein are oligonucleotides antiparallel to the human plasminogen antigen activator mRNA. After hybridization of the oligomer-PAs to the RNA, the distance between the 3' ends of the $oligomer_{n-1}$ and the 5' ends of the $oligomer_n$ is equal to 0 nucleotides of plasminogen antigen activator mRNA. n as used herein is from 1 to 14.

H_2N-***MEEPQSDPSVEPPLSQETFSDLWKLLPENNVL***

Oligomer1-**PA**$_1$ is

L^1
5'-cccaatccctcttgcaactga-3'

Oligomer2-**PA**$_2$ is

H_2N-*SPLPSQAMDDLMLSPDDIEQWF*
L^2 L^1
5'- attctactacaagtctgccctt - 3'

Oligomer3-**PA**$_3$ is

H_2N-*TEDPGPDEAPRMPEAAPRVAPAPAAP*
L^2 L^1
5'-ttgtgaccggctccactg -3'

Oligomer4-**PA**$_4$ is

H_2N-*TPAAPAPAPSWPLSSSVPSQKTYQG*
L^2 L^1
5'-taccttggtacttctctaa -3'

Oligomer5-**PA**$_5$ is

H_2N-*SYGFRLGFLHSGTAKSVTCTY*
L^2 L^1
5'-atgccatattagcccatcaga -3'

Oligomer6-**PA**$_6$ is

H_2N-*SPALNKMFCQLAKTCPVQLWVDSTPPPG*
L^2 L^1
5'- ccaagcattctgtccctcctttt-3'

Oligomer7-**PA**$_7$ is

H_2N-*TRVRAMAIYKQSQHMTEVVRRCPHHE*
L^2 L^1
5'- tccggtccggagcacca-3'

Oligomer8-**PA**$_8$ is

H_2N-*TCSDSDGLAPPQHLIRVEGNLRVEYLDDRN*
L^2 L^1
5'-gccatgacctgtatgttaca - 3'

Oligomer9-**PA**$_9$ is

H_2N-*TFRHSVVVPYEPPEVGSDCTTIHYNYMCN*
L^2 L^1
5'- ggtgtgggaaagttagcggg-3'

Oligomer10-**PA**$_{10}$ is

H_2N-*SSCMGGMNRRPILTIITLEDSSGNLLGRN*
L^2 L^1
5'- gcgaattccaaatgattttaa-3'

Oligomer11-**PA**$_{11}$ is

H_2N-*SFEVRVCACPGRDRRTEEENLRKKGEPHHELPPG*
L^2 L^1
5'- aatgtgaacatgaataa-3'

Oligomer12-**PA**$_{12}$ is

H_2N-*STKRALPNNTSSSPQPKKKPLDGEYF*
L^2 L^1
5'- agagtgggatacagcatctata-3'

Oligomer$_{13}$-**PA**$_{13}$ is H_2N-*TLQIRGRERFEMFRELNEALELKDAQAGKEPGG*
L^2 L^1
5'-acaaaaccattccactctgatt-3'

Oligomer$_{14}$-**PA**$_{14}$ is H_2N-*SRAHSSHLKSKKGQSTSRHKKLMFKTEGPDSD*
L^2
5'-ttggaaaaactgtgaaaaa-3'

The oligomer$_n$-**PA**$_n$ (n is selected from 1 to 14) are peptides chemically bound to oligomers which can form stable duplex structure with the plasminogen antigen activator mRNA expressed in human ovarian tumour cells. Using the plasminogen antigen activator mRNA it is possible to synthesize any other protein or small BAC. All these proteins or BACs will be synthesized only in those cells where the human plasminogen activator mRNA is expressed. In the case of the human plasminogen activator mRNA, the synthesis of the protein or BAC will occur only in ovarian tumour cells. Oligomer 1 at its 3' end is bound to the "C" end of the peptide **PA**$_1$ of p53 through the linking moiety L^1. Oligomers 2 to 13 are bound at their 5' and 3' ends to peptides **PA**$_2$ to **PA**$_{13}$ at their "N" and "C" ends respectively, through the linking moieties L^2 and L^1. Oligomer14 at it's 5' end is bound to the "N" end of the peptide **PA**$_{14}$ of p53 through the linking moiety L^2. The first methionine of **PA**$_1$ is formylated, and the amino end of peptide$_1$ is not bound to Oligomer$_1$. The last amino acid at the carboxyl end of **PA**$_{14}$ is not bound to Oligomer$_{14}$. Only 14 peptides chemically bound to 14 oligomers are required to synthesize p53 tumour suppresser specifically in the cells of the ovarian tumour. In any type of tumour cell RNAs specific to this cell type are expressed. By this method, it is possible to synthesise any protein or BACs described above on these RNAs.

The 14 **Oligomer-PA**s are hybridized on the mRNA in such a manner that the 3' end of the oligomer$_1$-**PA**$_1$ is located at a distance from the 5' end of the oligomer$_2$-**PA**$_2$ which is equal to 0 nucleotides of the plasminogen antigen activator mRNA. The distance between the 5' end of the Oligomer$_3$-**PA**$_3$ and the 3' end of the Oligomer$_2$-**PA**$_2$ is equal to 0 nucleotides of the plasminogen antigen activator mRNA. The distance between the 5' end of the Oligomer$_4$-**PA**$_4$ and the 3' end of the oligomer$_3$-**PA**$_3$ is equal to 0

nucleotides of the plasminogen antigen activator mRNA etc. In other words after hybridization of the oligomer-**PA**s to the plasminogen antigen activator mRNA, the distance between the 3' end of the oligomer$_{n-1}$-**PA**$_{n-1}$ and the 5' end of the Oligomer$_n$-**PA**$_n$ is equal to 0 nucleotides of the plasminogen antigen activator mRNA.

After the degradation of the oligomers and/or linking moieties, the synthesized protein p53 is released into the determined cells.

{H_2N-**PA**$_1$-C(O)NH-**PA**$_2$-C(O)NH-**PA**$_3$-C(O)NH-**PA**$_4$-C(O)NH-**PA**$_5$-C(O)NH-**PA**$_6$--C(O)NH-**PA**$_7$-C(O)NH-**PA**$_8$-C(O)NH-**PA**$_9$-C(O)NH-**PA**$_{10}$-C(O)NH-**PA**$_{11}$-C(O)NH--**PA**$_{12}$-C(O)NH-**PA**$_{13}$-C(O)NH-**PA**$_{14}$-COOH} is biologically active protein - tumour suppresser p53. The yield of synthesis in the cells can be very low, even <1%, because the synthesis occurs directly into the targeted cells. Using different RNAs transcribed at different levels in the same cells, it is possible change the amount of the protein synthesized by this method.

The variety of proteins , which can be synthesized by the proposed method, is enormous. Limitations could occur if the proteins to be synthesised are very large or have many hydrophobic amino acids.

The distance between the 5' and 3' ends of the oligomer-**PA**s after hybridization to the template can be varied between 0 and 10 nucleotides of the target RNA.

In the example described above, the oligomers are antiparallel to the plasminogen antigen activator mRNA. Using RNAs which expressed specifically in different tumour cells, the synthesis of any protein in these cells can be achieved. One example of such RNA is metastasin (mts-1) mRNA (Tulchinsky et al.1992, accession number g486654).

Using oligomers antiparallel to metastasin mRNA it is possible to synthesise any toxin or protein specifically in human metastatic cells.

Using different RNAs expressed specifically in different tissues or in cells infected by viruses, or in bacterial cells, it is possible to synthesise any toxin or protein specifically in these cells.

The example 10

Synthesis of the tumour suppresser p53 according to Formula 7. After hybridization of the oligomer-**PA**s to mRNA specific to

ovarian tumour cells (NbHOT Homo sapiens mRNA accession number AA402345), the chemical moiety K^1 of PA_2 (in this example K^1 is NH_2 group) interacts with the linking moiety L^2 of the oligomer$_1$-PA_1. After the interaction has occurred, the peptide **PA**$_1$ is bound through the peptidyl bond to the peptide **PA**$_2$ and is released from the 5' end of the oligomer$_1$. The linking moiety L^2 of the oligomer$_1$ is activated so that it interacts with the linking moiety L^1 of oligomer$_2$, and the peptide **PA**$_1$-C(O)NH-**PA**$_2$ is released from the 3' end of oligomer$_2$. The chemical moiety K^1 of oligomer$_3$-**PA**$_3$ interacts with the linking moiety L^2 of oligomer$_2$-{**PA**$_1$-C(O)NH-**PA**$_2$} to bind peptide **PA**$_3$ with **PA**$_1$-C(O)NH-**PA**$_2$, releasing peptide **PA**$_1$-C(O)NH-**PA**$_2$-C(O)NH-**PA**$_3$ from oligomer$_2$. The activated linking moiety L^2 of oligomer$_2$ interacts with the linking moiety L^1 and releases the peptide **PA**$_1$-C(O)NH-**PA**$_2$-C(O)NH-**PA**$_3$ from the 3' ends of oligomer$_3$. The processes described above are repeated in the cells 13 times. In such as manner, the protein: {**PA**$_1$-C(O)NH-**PA**$_2$-C(O)NH-**PA**$_3$-C(O)NH-**PA**$_4$-C(O)NH-**PA**$_5$-C(O)NH-**PA**$_6$-C(O)NH-**PA**$_7$-C(O)NH-**PA**$_8$-C(O)NH-**PA**$_9$-C(O)NH-**PA**$_{10}$-C(O)NH-**PA**$_{11}$-C(O)NH-**PA**$_{12}$-C(O)NH-**PA**$_{13}$-C(O)NH-**PA**$_{14}$} can be synthesized. Neither the degradation of the oligomers nor the degradation of the linking moieties is necessary to release the protein from the oligomers. Peptidyl bond formation between **Pa**$_{n-1}$ and **PA**$_n$ and degradation of the linking moieties L^2 proceed simultaneously with the release of **PA**s from the 5' ends of the oligomers. The activated linking moieties L^2 interact with the linking moieties L^1 to release the bound peptides from the 3' ends of the oligomers.

PA$_1$ -***MEEPQSDPSVEPPLSQETFSDLWKLLPENNVL***

PA$_2$ -***SPLPSQAMDDLMLSPDDIEQWF***

PA$_3$ -***TEDPGPDEAPRMPEAAPRVAPAPAAP***

PA$_4$ -***TPAAPAPAPSWPLSSSVPSQKTYQG***

PA$_5$ -***SYGFRLGFLHSGTAKSVTCTY***

PA$_6$ -***SPALNKMFCQLAKTCPVQLWVDSTPPPG***

PA$_7$- ***TRVRAMAIYKQSQHMTEVVRRCPHHE***

PA$_8$ - ***TCSDSDGLAPPQHLIRVEGNLRVEYLDDRN***

PA$_9$ - ***TFRHSVVVPYEPPEVGSDCTTIHYNYMCNS***

PA$_{10}$ - ***SCMGGMNRRPILTIITLEDSSGNLLGRN***

PA$_{11}$ -***SFEVRVCACPGRDRRTEEENLRKKGEPHHELPPG***

PA_{12} -*STKRALPNNTSSSPQPKKKPLDGEYF*

PA_{13} -*TLQIRGRERFEMFRELNEALELKDAQAGKEPGG*

PA_{14} -*SRAHSSHLKSKKGQSTSRHKKLMFKTEGPDSD*

where PA_1 to PA_{14} are peptides bound to oligomers,

Amino acids are designated in bold/italicised one letter code. ***A*** - alanine, ***R*** - arginine, ***N*** - asparagine, ***D*** - aspartic acid, ***C***- cysteine, ***Q*** -glutamine, ***E*** - glutamic acids, ***G*** - glycine, ***H*** - histidine, ***I*** -isoleucine, ***L***-leucine, ***K*** - lysine, ***M*** - methionine, ***F*** - phenylalanine, ***P***- proline, ***S*** - serine, ***T*** - threonine, ***W***- tryptophan, ***Y*** - tyrosine, ***V*** - valine.

$Oligomer_1$	**3' ATGGGCGGTAGGTAC 5'**
$Oligomer_2$	**3' TAGCGGTGCCCTCGA 5'**
$Oligomer_3$	**3' AACCCCGACGTCACG 5'**
$Oligomer_4$	**3' TTCCGGACCCACGGA 5'**
$Oligomer_5$	**3' CGAGGTACAGGCCCC 5'**
$Oligomer_6$	**3' TACTCGAGTGTCTCG 5'**
$Oligomer_7$	**3' ACGACCGTCCCTAGT 5'**
$Oligomer_8$	**3' GACCGTGACTTCACC 5'**
$Oligomer_9$	**3' TGACGGACGCCCGGA 5'**
$Oligomer_{10}$	**3' CAGTCCTCGTCTAGC 5'**
$Oligomer_{11}$	**3' TTCGACGTGAGTCCC 5'**
$Oligomer_{12}$	**3' TCTCGGAGTCCCTTC 5'**
$Oligomer_{13}$	**3' GGAGAGTCTGGTCGA 5'**
$Oligomer_{14}$	**3' GGTCGGGTCGCGGGT 5'**

Oligomers are complementary (antiparallel) to NbHOT Homo sapiens mRNA (clone 741045 accession number AA402345) which is specific to ovarian tumour cells. The distance of the oligomers each from other is null nucleotides of the NbHOT Homo sapiens mRNA.

$Oligomer_1$-PA_1 is *MEEPQSDPSVEPPLSQETFSDLWKLLPENNVL* L^2

3' ATGGGCGGTAGGTAC 5'

(K^1)*SPLPSQAMDDLMLSPDDIEQWF*

Oligomer$_2$-PA$_2$ is

L^1 L^2

3' TAGCGGTGCCCTCGA 5'

Oligomer$_3$-PA$_3$ is

(K^1)*TEDPGPDEAPRMPEAAPRVAPAPAAP*

L^1 L^2

3' AACCCCGACGTCACG 5'

Oligomer$_4$-PA$_4$ is

(K^1)*TPAAPAPAPSWPLSSSVPSQKTYQG*

L^1 L^2

3' TTCCGGACCCACGGA 5'

Oligomer$_5$-PA$_5$ is

(K^1)*SYGFRLGFLHSGTAKSVTCTY*

L^1 L^2

3' CGAGGTACAGGCCCC 5'

Oligomer$_6$-PA$_6$ is

(K^1)*SPALNKMFCQLAKTCPVQLWVDSTPPPG*

L^1 L^2

3' TACTCGAGTGTCTCG 5'

Oligomer$_7$-PA$_7$ is

(K^1)*TRVRAMAIYKQSQHMTEVVRRCPHHE*

L^1 L^2

3' ACGACCGTCCCTAGT 5'

Oligomer$_8$-PA$_8$ is

(K^1)*TCSDSDGLAPPQHLIRVEGNLRVEYLDDRN*

L^1 L^2

3' GACCGTGACTTCACC 5'

Oligomer$_9$-PA$_9$ is

(K^1)*TFRHSVVVPYEPPEVGSDCTTIHYNYMCNS*

L^1 L^2

3' TGACGGACGCCCGGA 5'

Oligomer$_{10}$-PA$_{10}$ is

(K^1)*SCMGGMNRRPILTIITLEDSSGNLLGRNS*

L^1 L^2

3' CAGTCCTCGTCTAGC 5'

Oligomer$_{11}$-PA$_{11}$ is

(K^1)*FEVRVCACPGRDRRTEEENLRKKGEPHHELPPGS*

L^1 L^2

3' TTCGACGTGAGTCCC 5'

(K^1)*TKRALPNNTSSSPQPKKKPLDGEYF*

Oligomer$_{12}$-PA$_{12}$ is

L^1 L^2

3' TCTCGGAGTCCCTTC5'

(K^1)*TLQIRGRERFEMFRELNEALELKDAQAGKEPGG*

Oligomer$_{13}$-PA$_{13}$ is

L^1 L^2

3' GGAGAGTCTGGTCGA 5'

(K^1)*SRAHSSHLKSKKGQSTSRHKKLMFKTEGPDSD*

Oligomer$_{14}$-PA$_{14}$ is

L^1

3' GGTCGGGTCGCGGGT 5'

This method of protein synthesis also allows modification of the synthesized protein. Certain amino acids of the peptides used in the synthesis can be glycosylated or phosphorylated.

Glycosylation of a protein is a complex process, and difficulties may occur in the penetrance of some tissues with the glycosylated form of the peptide due to the size of the molecule.

However the use of phosphorylated peptides opens up the possibility to synthesize already active proteins in the cells of living organisms.

The synthesis of RNA.

Using the method described above, it is possible to synthesise into targeted cells not only proteins but also RNAs. An example of such synthesis is represented in Fig.10

To synthesize whole RNA in cells from n oligomers bound to oligoribonucleotides (oligomer-PAs) the concentration of such oligomer-PAs must be high. After the simultaneous hybridization of **oligomer-PAs** to the same molecule of the cellular RNA, the chemically active 3' hydroxyl group of the oligoribonucleotide **PA**$_1$ interacts with the linking moiety -L^2-S- which bound oligoribonucleotide **PA**$_2$ with oligomer 2. In this case the linking group is represented with an -S-L^2- moiety which is coupled to phosphate group of the oligoribonucleotide **PA**$_2$. The 3' hydroxyl group of the oligoribonucleotide **PA**$_1$ interacts with the linking group of **PA**$_2$ forming a chemical bond with the phosphate group, releasing the oligoribonucleotide **PA**$_2$ at it's 5' end from oligomer 2, and activating the linking moiety with the formation of the -SH group. This chemically active group -SH

interacts with linking moiety -L^1-S which couples the oligomers. This process is repeated n-1 times to bind all PAs in one molecule. **PA**$_1$ is bound through chemical moiety -O- to **PA**$_2$, then in turn **PA**$_1$-m-**PA**$_2$ is bound through chemical moiety -O- to **PA**$_3$, then **PA**$_1$-m-**PA**$_2$-m-**PA**$_3$ is bound through chemical moiety -O- to **PA**$_4$ and so on until the last oligoribonucleotide is bound, forming whole biologically active RNA.

In this figure "**PA**$_n$" are oligoribonucleotides comprising from 3 to 300 nucleotides.

n in "**PA**$_n$" means the ordinal number in a series of oligoribonucleotides used in the synthesis of a whole RNA, where n is selected from 2 to 1000.

Claims:

1. A process for synthesis of biologically active compounds (BACs) from biologically inactive BAC precursors (**PBACs**) "**A**", "**B**" and "**PA**$_n$" chemically bound to 5' and/or 3' ends of the oligomers directly in cells of living organisms according to Formulas 1 to 7, which process comprises:

(a) at least two oligomers, chemically bound at their 5' and/or 3' ends to biologically inactive precursors of the biologically active compounds (oligomer-**PBACs**), are hybridised simultaneously to cellular RNA, DNA or dsDNA in vivo in cells of a living organism, so that after hybridization the distance between the 5' or 3' ends of the oligomer-**PBAC** "**A**" and the 3' or 5' ends of the oligomer-**PBAC** "**B**" is from 0 to 8 ribo(deoxy)nucleotides of cellular RNA, DNA or dsDNA correspondingly, and the chemically active groups K^2 and K^1 of the biologically inactive **PBACs** "**A**" and "**B**" can interact with each other or with linking moieties L^1 and L^2 to form chemical moiety "m" between **PBAC** "**A**" and **PBAC** "**B**" so that "**A**"-m-"**B**" is equal to the biologically active compound "T";

(b) (**Formula 1**) the same process as in (a), but after hybridization of the "oligomer-**PBACs**" "**A**" and "**B**" to cellular RNA, DNA or dsDNA, the chemically active groups K^1 and K^2 of the oligomer-PBACs "A" and "B" interact with each other to form the chemical moiety "m", which combines PBACs "**A**" and "**B**" into one active molecule of the biologically active compound "**T**", the degradation of the oligomers and/or linking moieties L^1 and L^2 by cellular enzymes or hydrolysis leads to the release of the synthesized BAC "T" directly into targeted cells of a living organism;

(c) (**Formula 2**) the same process as in (a), but after hybridization of "oligomer-**PBACs**" "**A**" and "**B**" to cellular RNA, DNA or dsDNA, the chemically active group K^2 of oligomer-**PBAC** "**B**" interacts with the linking moiety L^1 of oligomer-**PBAC** "**A**" to combine the **PBACs** through chemical moiety "m", into one active molecule of the biologically active compound "T", releasing the **PBAC** "B" from the

oligomer and the oligomer "A" and/or linking moieties L^1 are degraded by cellular enzymes or hydrolysis leading to the release of the synthesized BAC "T" directly into targeted cells of a living organism;

(d) (**Formula 3**) the same process as in (a), but after hybridization of "oligomer-**PBAC**s" "**A**" and "**B**" to cellular RNA, DNA or dsDNA, the chemically active group K^1 of the oligomer-**PBAC**s interacts with the linking moiety L^2 to combine the **PBAC**s through chemical moiety "m" into one active molecule of the biologically active compound "T", releasing the **PBAC** "**B**" from the oligomer and activating the chemical moiety L^2, which after activation interacts with the linking moiety L^1 to release the biologically active compound "T" from oligomer directly into targeted cells of a living organism.

(e)(**Formula 4**) the same process as in (a), but after hybridization of "oligomer-**PBAC**s" "**A**" and "**B**" to cellular RNA, DNA or dsDNA, the chemically active group K^2 of oligomer-**PBAC** "**B**" interacts with the linking moiety L^1 of the oligomer-**PBAC** "**A**" to combine the **PBAC**s through the chemical moiety "m", and the chemically active group K^1 of the oligomer-**PBAC** "**A**" interacts with the linking moiety L^2 of the oligomer-**PBAC** "**B**" to form chemical moiety m^1 which, together with the chemical moiety m, combines two "**PBAC**s" into one active molecule of the biologically active compound "**T**", with the release of the **PBAC** "**B**" from the oligomer.

2.The process of claim 1 but:

(a) the synthesis of the BAC "**PR**" in the cells of living organisms is performed from n "oligomer$_n$-**PA**$_n$"s so that "oligomer$_{n-1}$-**PA**$_{n-1}$" and "oligomer$_n$-**PA**$_n$" are hybridized simultaneously on the same molecule of cellular RNA, DNA or dsDNA, with a distance of from null to eight nucleotides of cellular RNA or DNA between the 3' or 5' ends of the oligomer$_{n-1}$-"**PA**$_{n-1}$", and the 5' or 3' ends of the oligomer$_n$-"**PA**$_n$" correspondingly, here n is selected from 2 to 2000;

(b) (**Formula 5**) the same process as in (a), but after simultaneous hybridization of "oligomer$_{n-1}$-**PA**$_{n-1}$" and

"oligomer$_n$-**PA**$_n$" to cellular RNA or DNA, the chemically active groups K^1 and K^2 interact with each other to form the chemical moiety "m" between "oligomer$_{n-1}$-**PA**$_{n-1}$" and "oligomer$_n$-**PA**$_n$" correspondingly, this step is repeated in the cells n-1 times and combines n-1 times all "**PA**$_n$"s into one active molecule of biologically active compound "PR" which consists of n **PA**$_n$ so that the compound {"**PA**"$_1$-m-"**PA**"2-m-"**PA**"3-m-"**PA**"4-m-...-m-"**PA**$_{n-3}$"-m-"**PA**$_{n-2}$"-m-"**PA**$_{n-1}$"-m-"**PA**$_n$"} is the biologically active compound "PR"; the degradation of the oligomers and/or linking moieties L^1 and L^2 leads to the release of synthesized BAC "PR" directly in the targeted cells of a living organism, here n is selected from 2 to 2000;

(c) (**Formula 6**) the same process as in (a), but after simultaneous hybridization of "oligomer$_{n-1}$-**PA**$_{n-1}$" and "oligomer$_n$-**PA**$_n$" to cellular RNA, DNA or dsDNA chemically active group K^1 of "oligomer$_{n-1}$-**PA**$_{n-1}$" interacts with the linking moiety L^2 of "oligomer$_n$-**PA**$_n$" to bind **PA**$_{n-1}$ and **PA**$_n$ through the chemical moiety "m", this step is repeated in the cells n-1 times, and combines n-1 times all **PA**$_n$s after hybridization of all n "**Oligomer$_n$-PA**$_n$"s into one active molecule of biologically active compound "PR", which consists of n **PA**$_n$ so that the compound {**PA**$_1$-m-**PA**$_2$-m-**PA**$_3$-m-**PA**$_4$-m-...-m-**PA**$_{n-3}$-m-**PA**$_{n-2}$-m-**PA**$_{n-1}$-m-**PA**$_n$} is equal to the biologically active compound PR; the degradation of the oligomers and/or linking moieties L^1 and L^2 due to cellular enzymes or hydrolysis leads to the release of the synthesized BAC "**PR**" directly into targeted cells of a living organism, here n is selected from 2 to 2000;

(d) (**Formula 7**) the same process as in (c), but after interaction of K^1 with L^2, L^2 is chemically activated so that it can interact with the linking moiety L^1 of oligomer-**PA**$_{n-1}$, destroying the binding of oligomer$_{n-1}$ with **PA**$_{n-1}$, this step is repeated n-1 times, so that only whole BAC "PR" consisting of n **PA**$_n$s {**PA**$_1$-m-**PA**$_2$-m-**PA**$_3$-m-**PA**$_4$-m-...-m-**PA**$_{n-3}$-m-**PA**$_{n-2}$-m-**PA**$_{n-1}$-m-**PA**$_n$} is released directly into targeted cells of a living organism, here n is selected from 2 to 2000.

3. In claims 1 and 2 the linking moieties L^1 and L^2 are bound to the first and/or last mononucleomers of the oligomers at their sugar or phosphate moiety, or directly to base, or to sugar moiety analogues, or to phosphate moiety analogues, or to base analogues.

4. In claim 1, biologically inactive precursors of BAC "**A**" and "**B**" are selected from chemical substances which can be bound to each other through the chemical moiety "m", so that the compound A-m-B is the biologically active compound "T":

A-O-**B**	is equal to a whole BAC	"**T**"
A-NH-C(O)-**B**	is equal to a whole BAC	"**T**"
A-C(O)-NH-**B**	is equal to a whole BAC	"**T**"
A-C(O)-**B**	is equal to a whole BAC	"**T**"
A-C(S)-**B**	is equal to a whole BAC	"**T**"
A-NH-**B**	is equal to a whole BAC	"**T**"
A-dbdN--**B**	is equal to a whole BAC	"**T**"
A-C(O)O-**B**	is equal to a whole BAC	"**T**"
A-C(O)S-**B**	is equal to a whole BAC	"**T**"
A-C(S)S-**B**	is equal to a whole BAC	"**T**"
A-S-S-**B**	is equal to a whole BAC	"**T**"
A-C(S)O-**B**	is equal to a whole BAC	"**T**"
A-N=N-**B**	is equal to a whole BAC	"**T**"

5. In claim 2, biologically inactive precursors of BAC PA_n are selected from biologically inactive peptides and oligoribonucleotides so that the compound {"$\mathbf{PA_1}$"-m-"$\mathbf{PA_2}$"-m-"$\mathbf{PA_3}$"-m-...-m-"$\mathbf{PA_{n-2}}$"-m-"$\mathbf{PA_{n-1}}$"-m-"$\mathbf{PA_n}$"} is equal to the biologically active compound "PR", which is a protein or a RNA.

6.Chemical moieties in claims 1, 2,3 and 4 are as follows:

m is selected independently from: -S-S-, -N(H)C(O)-, -C(O)N(H)-, -C(S)-O-, -C(S)-S-, -O-, -N=N-, -C(S)-, -C(O)-O-, -NH-, -S-;

K^1 is selected independently from: -NH(2), dbdNH, -OH, -SH, -F, -Cl, -Br, -I, -R^1-C(X)-X^1-R^2;

K^2 is selected independently from: - NH(2), -dbd-NH, -OH, -SH, -R^1-C(X)-X^1-R^2, -F, -Cl, -Br, -I;

L^1 is independently: chemical bond, -R^1-,-R^1-O-S-R^2-, -R^1-S-O-R^2-, -R^1-S-S-R^2-, -R^1-S-N(H)-R^2-, -R^1-N(H)-S-R^2-, -R^1-O-N(H)-R^2-, -R^1-N(H)-O-R^2-, -R^1-C(X)-X-R^2-;

L^2 is independently: chemical bond, -R^1-, -R^1-O-S-R^2-, -R^1-S-O-R^2-, -R^1-S-S-R^2-, -R^1-S-N(H)-R^2-, -R^1-N(H)-S-R^2-, -R^1-O-N(H)-R^2-, -R^1-N(H)-O-R^2-, -R^1-C(X)-X^1-R^2-, -R^1-X-C(X)-X-C(X)-X-R^2-;

R^1 is independently: chemical bond, alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl, cycloheteroaryl, carbocyclic, heterocyclic ring, X^1-P(X)(X)-X^1, -S(O)-, -S(O)(O)-, -X^1-S(X)(X)-X^1-, -C(O)-, -N(H)-, -N=N-, -X^1-P(X)(X)-X^1-, -X^1-P(X)(X)-X^1-P(X)(X)-X^1, -X^1-P(X)(X)-X^1-P(X)(X)-X^1-P(X)(X)-X^1, -C(S)-, any suitable linking group;

R^2 is independently chemical bond, alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl, cycloheteroaryl, carbocyclic, heterocyclic ring, X^1-P(X)(X)-X^1, -S(O)-, -S(O)(O)-, -X^1-S(X)(X)-X^1-, -C(O)-, -N(H)-, -N=N-, -X^1-P(X)(X)-X^1-, -X^1-P(X)(X)-X^1-P(X)(X)-X^1, -X^1-P(X)(X)-X^1-P(X)(X)-X^1-P(X)(X)-X^1, -C(S)-, any suitable linking group;

X is independently S, O, NH, Se, alkyl, alkenyl, alkynyl;
X^1 is independently S, O, NH, Se, alkyl, alkenyl, alkynyl.

7. Biologically active compound "T" which can be synthesized according the processes presented in claims 1 and 3 include but are not limited to:

a) biologically active alkaloids and their chemical analogues, peptides and inhibitors or cofactors of cellular enzymes;

b) synthetic and natural compounds which are inhibitors or stimulators of cellular processes such as:

cellular metabolism, DNA replication, RNA transcription, RNA translation, RNA elongation and RNA processing, protein synthesis, protein processing, cellular differentiation, cellular division, ion channel transmission, cellular protein and RNA's transportation, processes of cellular oxidation and the like.

8. Biologically active compounds "**T**" and "**PR**" in claims 1, 2, 3 and 4 include but are not limited to cytolitical toxins and toxins.

9. Biologically active compounds "**PR**" which are synthesized according to the processes presented in claims 2 and 4 are selected from biologically active proteins and RNAs.

10. The biologically active proteins and peptides described in claims 2,4 and 8 are synthesized from shorter biologically inactive peptides (PAs) consisting of from 2 to 100 aminoacids and their synthetic analogues L, D or DL configuration at the alpha carbon atom which are selected from valine, leucine, alanine, glycine, tyrosine, tryptophan, tryptophan isoleucine, proline, histidine, lysin, glutamic acid, methionine, serine, cysteine, glutamine phenylalanine, methionine sulfoxide, threonine, arginine, aspartic acid, asparagin, phenylglycine, norleucine, norvaline, alpha-aminobutyric acid, O-methylserine, O-ethylserine, S-methylcysteine, S-benzylcysteine, S-ethylcysteine, 5,5,5-trifluoroleucine and hexafluoroleucine; other modifications of aminoacids are also possible, including but not limited to the addition of substituents at carbone atoms such as -OH, -SH, $-SCH_3$, $-OCH_3$, -F,-Cl,-Br, $-NH_2$, -C(S)- or -C(O)-.

11. The biologically active proteins described in claims 8 and 9 include but are not limited to enzymes, DNA polymerases, RNA polymerases, esterases, lipases, proteases, kinases, transferases, transcription factors, transmembrane proteins, membrane proteins, cyclins, cytoplasmic proteins, nuclear proteins, toxins and like this.

12. The biologically active RNAs described in Formula 2 can be synthesized from biologically inactive oligoribonucleotides consisting of from 2 to 100 ribonucleotides, selected from uridin, guanidine, cytosin or adenine.

13. In claims 1 and 2, the cells where the biologically active substances can be synthesized have specific RNA, DNA or dsDNA molecules of determined sequence.

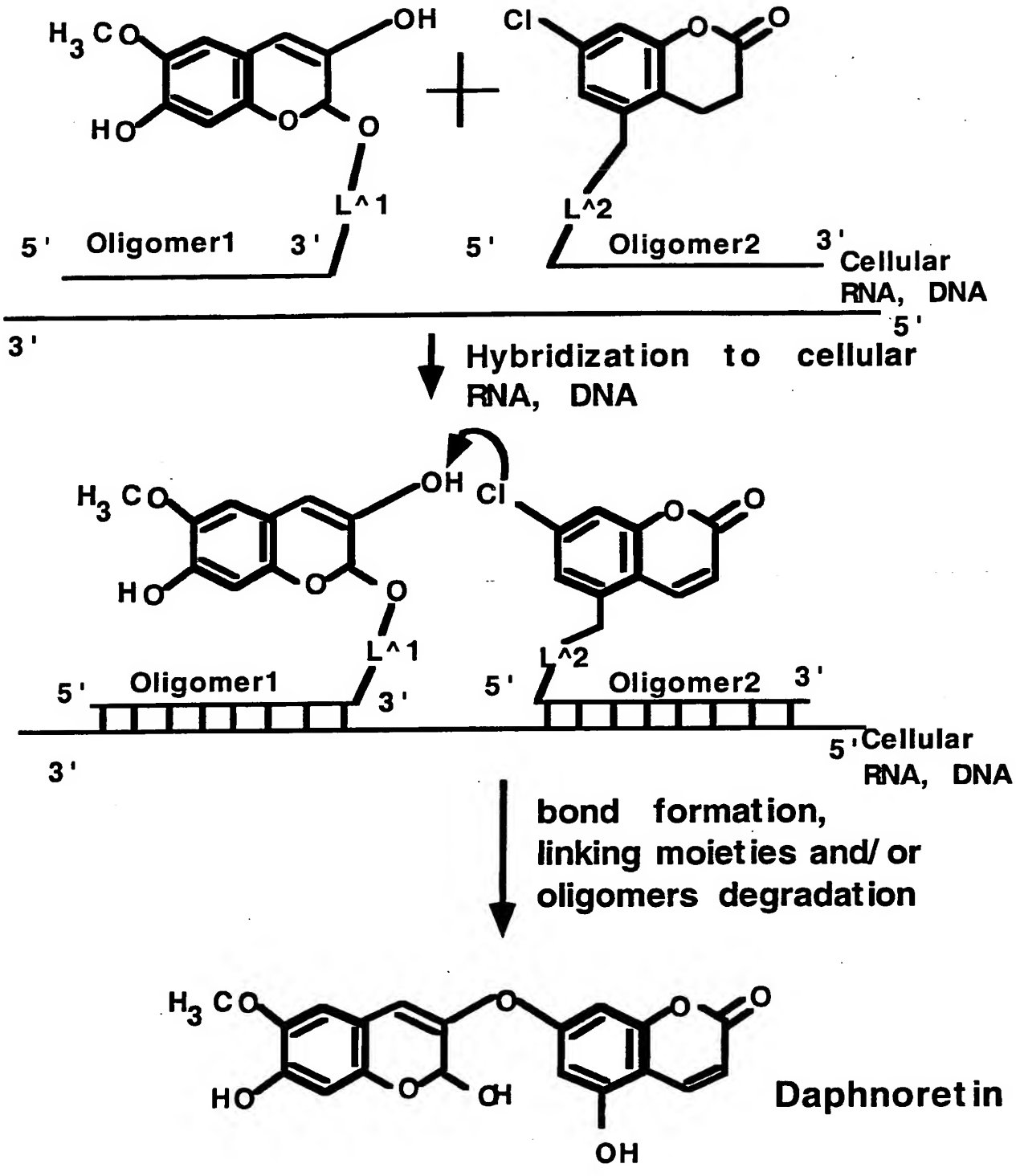

H3CO
OH
HO
O
O
L^1
5' Oligomer1 3'
Cl
O
O
L^2
5' Oligomer2 3'
Cellular RNA, DNA
5'
3'
Hybridization to cellular RNA, DNA
H3CO
OH
Cl
HO
O
O
L^1
L^2
5' Oligomer1 3'
5' Oligomer2 3'
3'
5' Cellular RNA, DNA
bond formation, linking moieties and/or oligomers degradation
H3CO
HO
OH
Daphnoretin

Fig. 1.

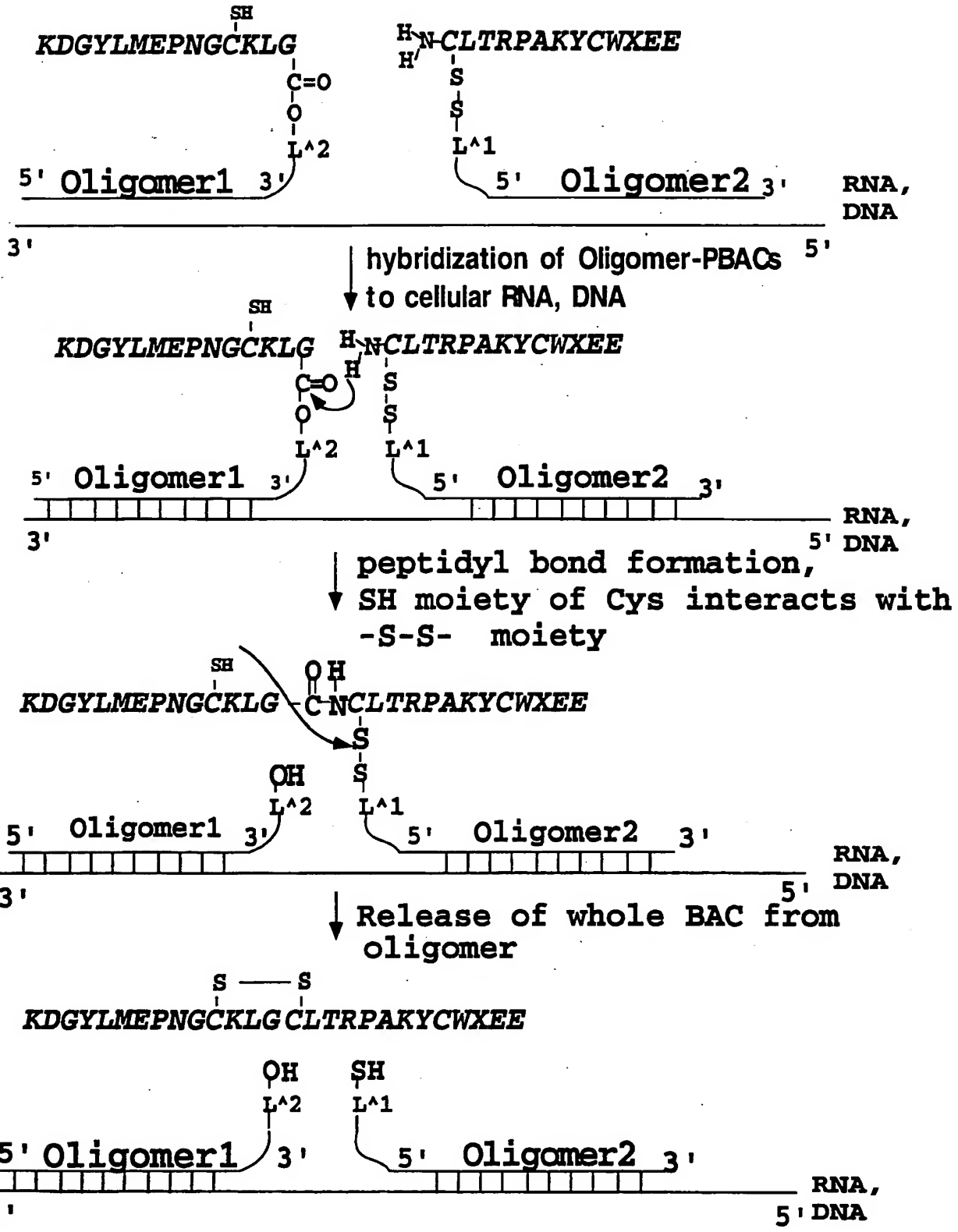

KDGYLMEPNGCKLG
CLTRPAKYCWXEE
Oligomer1
Oligomer2
RNA, DNA
hybridization of Oligomer-PBACs to cellular RNA, DNA
peptidyl bond formation, SH moiety of Cys interacts with -S-S- moiety
Release of whole BAC from oligomer

Fig. 2

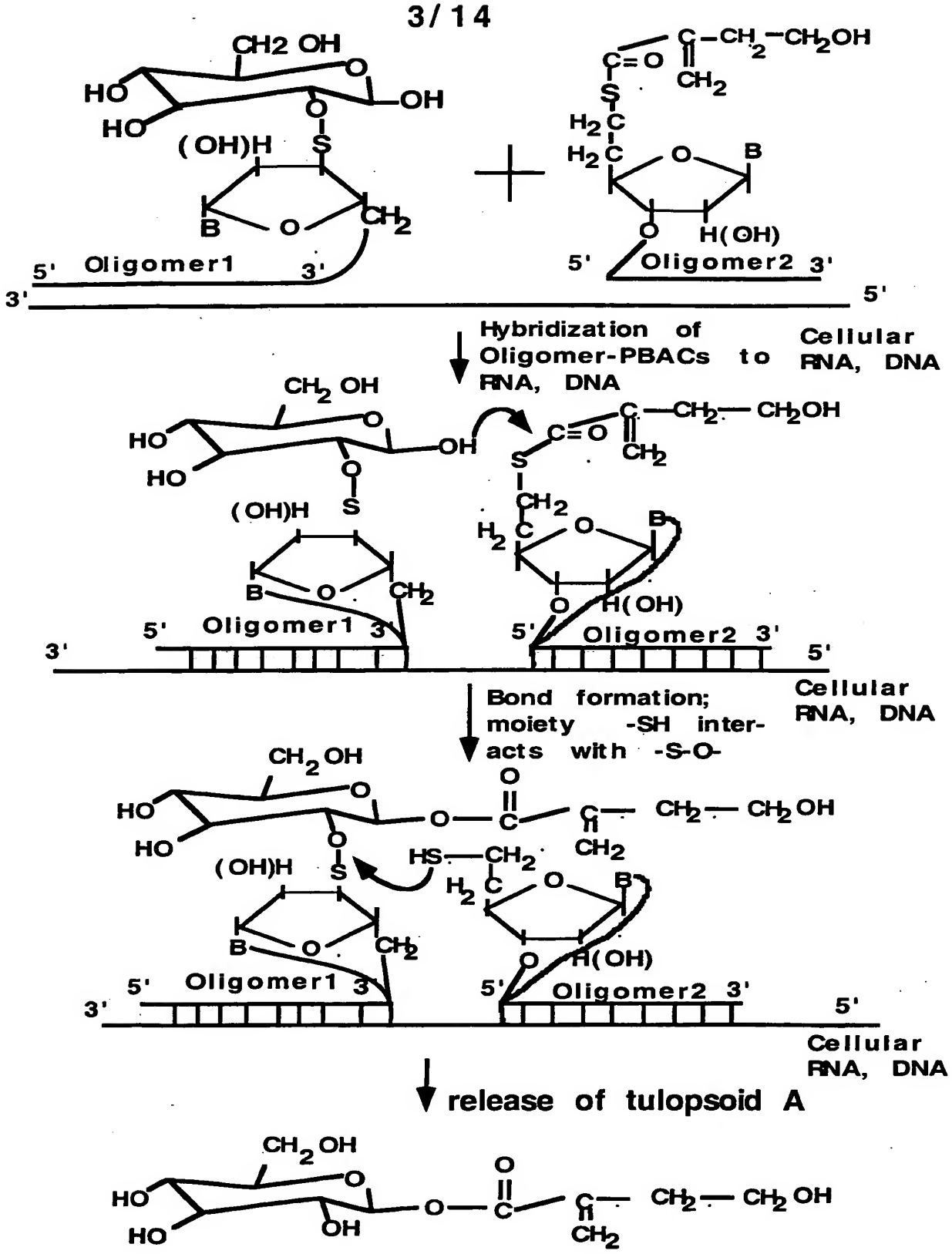

Oligomer1
Oligomer2
Hybridization of Oligomer-PBACs to RNA, DNA
Cellular RNA, DNA
Bond formation; moiety -SH interacts with -S-O-
Cellular RNA, DNA
release of tulopsoid A

Fig. 3.

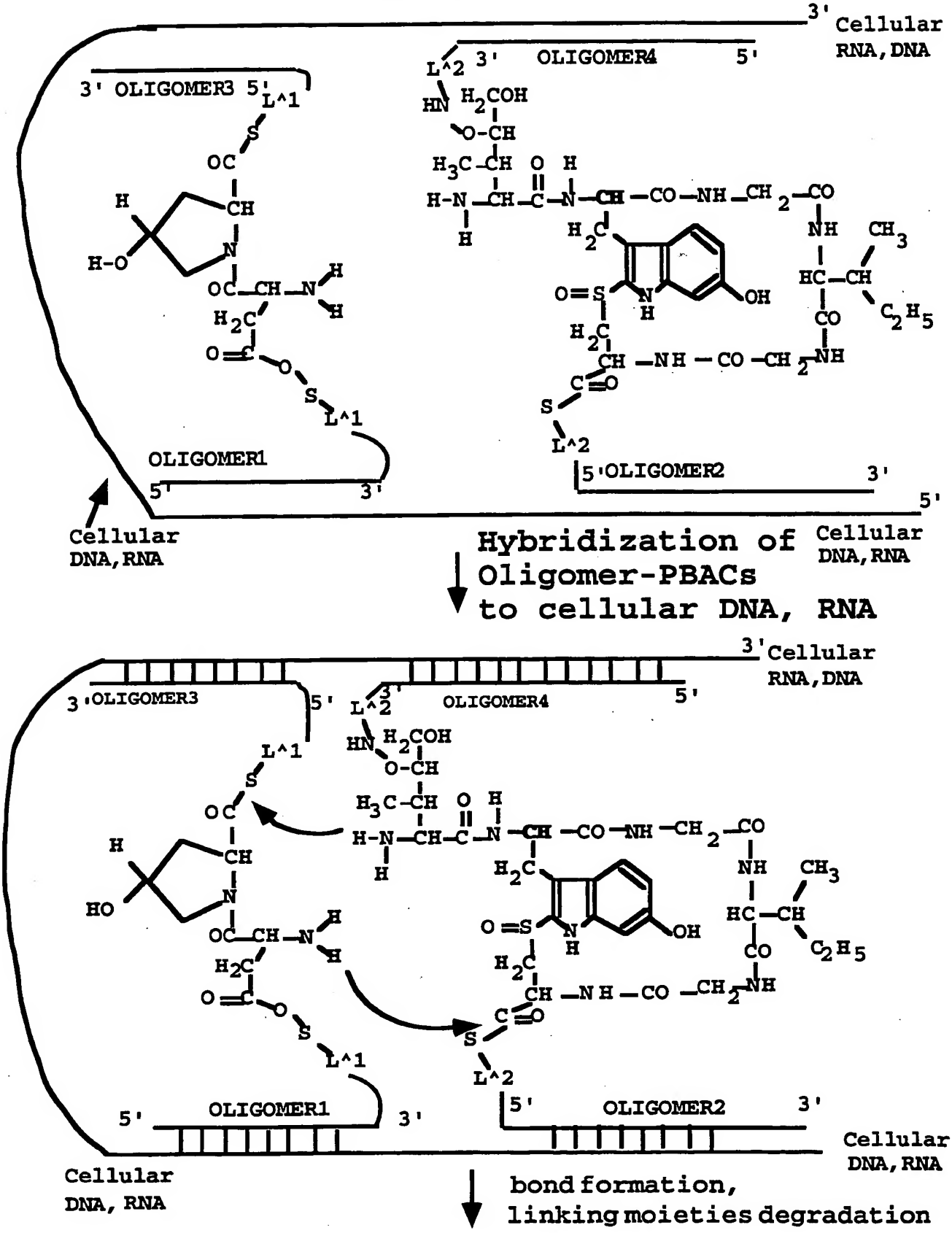

3' Cellular RNA, DNA
3' OLIGOMER3 5'
L^1
L^2 3' OLIGOMER4 5'
OLIGOMER1
5' 3'
5' OLIGOMER2 3'
5'
Cellular DNA, RNA
Hybridization of Oligomer-PBACs to cellular DNA, RNA
Cellular DNA, RNA
3' Cellular RNA, DNA
3' OLIGOMER3 5'
L^2 3' OLIGOMER4 5'
L^1
OLIGOMER1
5' 3'
5' OLIGOMER2 3'
Cellular DNA, RNA
Cellular DNA, RNA
bond formation, linking moieties degradation

Fig. 4

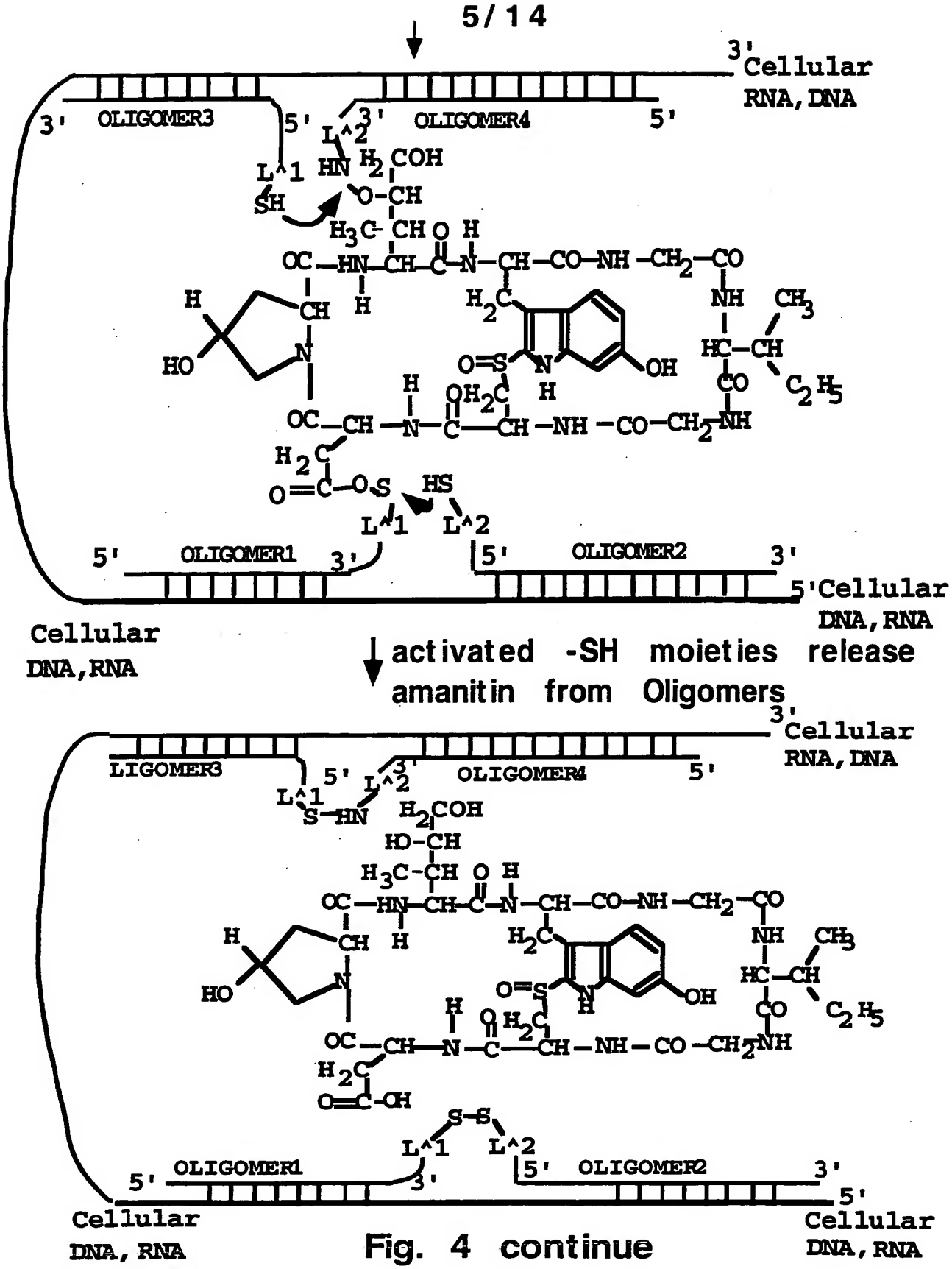


Fig. 4 continue

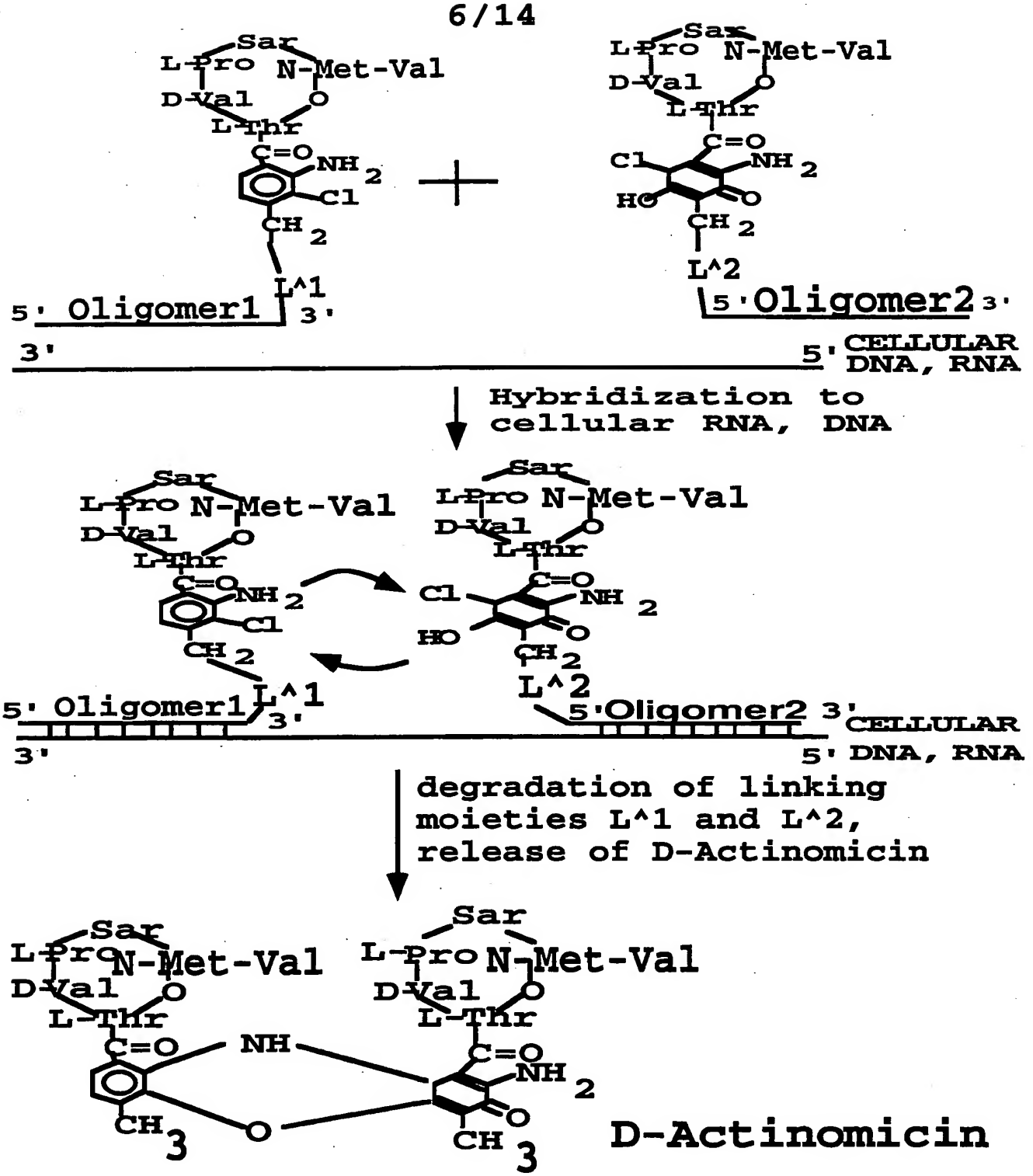

Sar
L-Pro
N-Met-Val
D-Val
L-Thr
C=O
NH 2
Cl
CH 2
L^1
5' Oligomer1 3'
3'
HO
L^2
5' Oligomer2 3'
5' CELLULAR DNA, RNA
Hybridization to cellular RNA, DNA
degradation of linking moieties L^1 and L^2, release of D-Actinomicin
CH 3
D-Actinomicin

Fig. 5.

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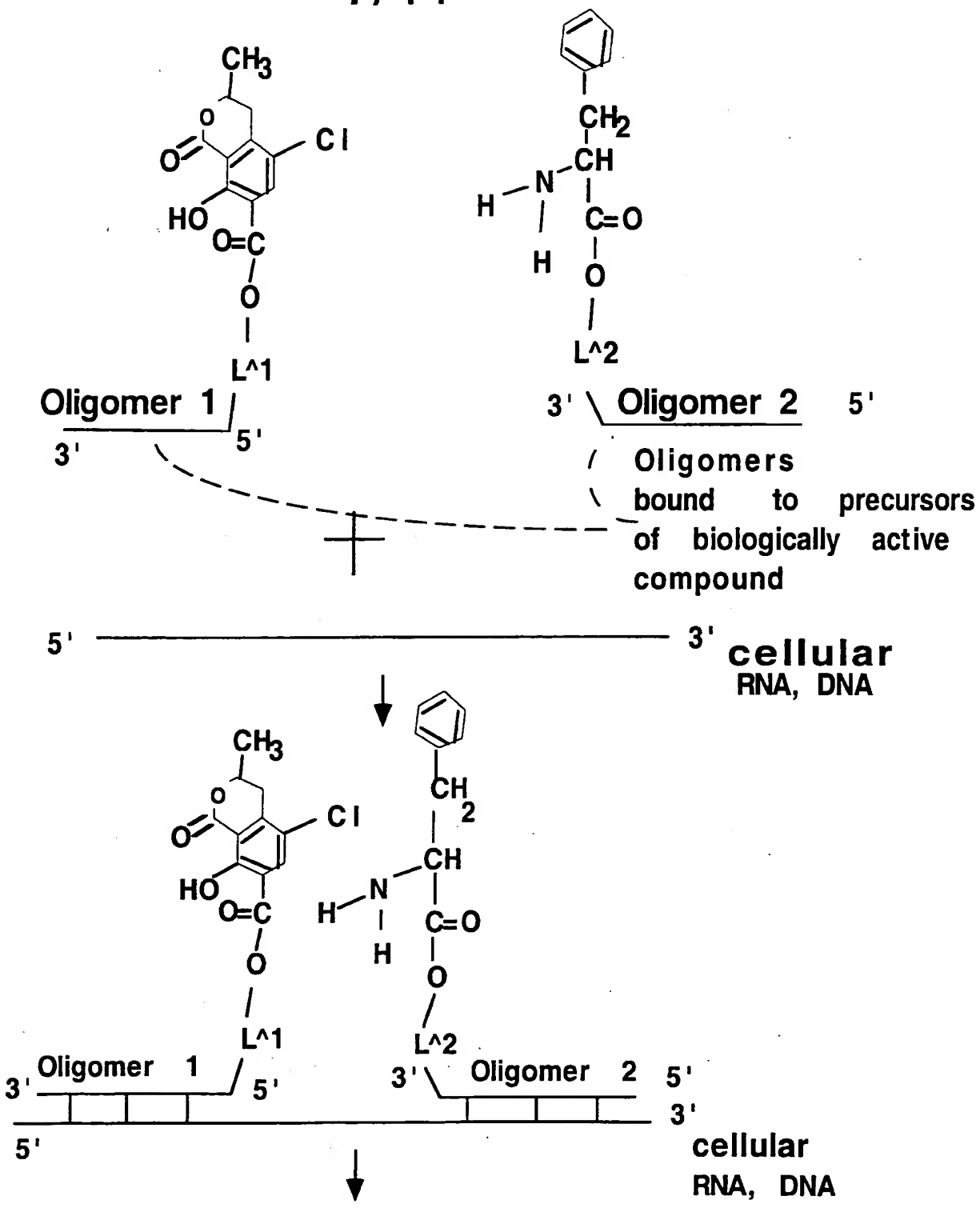
CH3
O
O
Cl
HO
O=C
O
L^1
Oligomer 1
3'
5'
CH2
CH
N
H
H
C=O
O
L^2
3'
Oligomer 2
5'
Oligomers bound to precursors of biologically active compound
5'
3'
cellular RNA, DNA
CH3
O
O
Cl
HO
O=C
O
L^1
Oligomer 1
3'
5'
CH2
2
CH
N
H
H
C=O
O
L^2
3'
Oligomer 2
5'
3'
5'
cellular RNA, DNA

Fig. 6

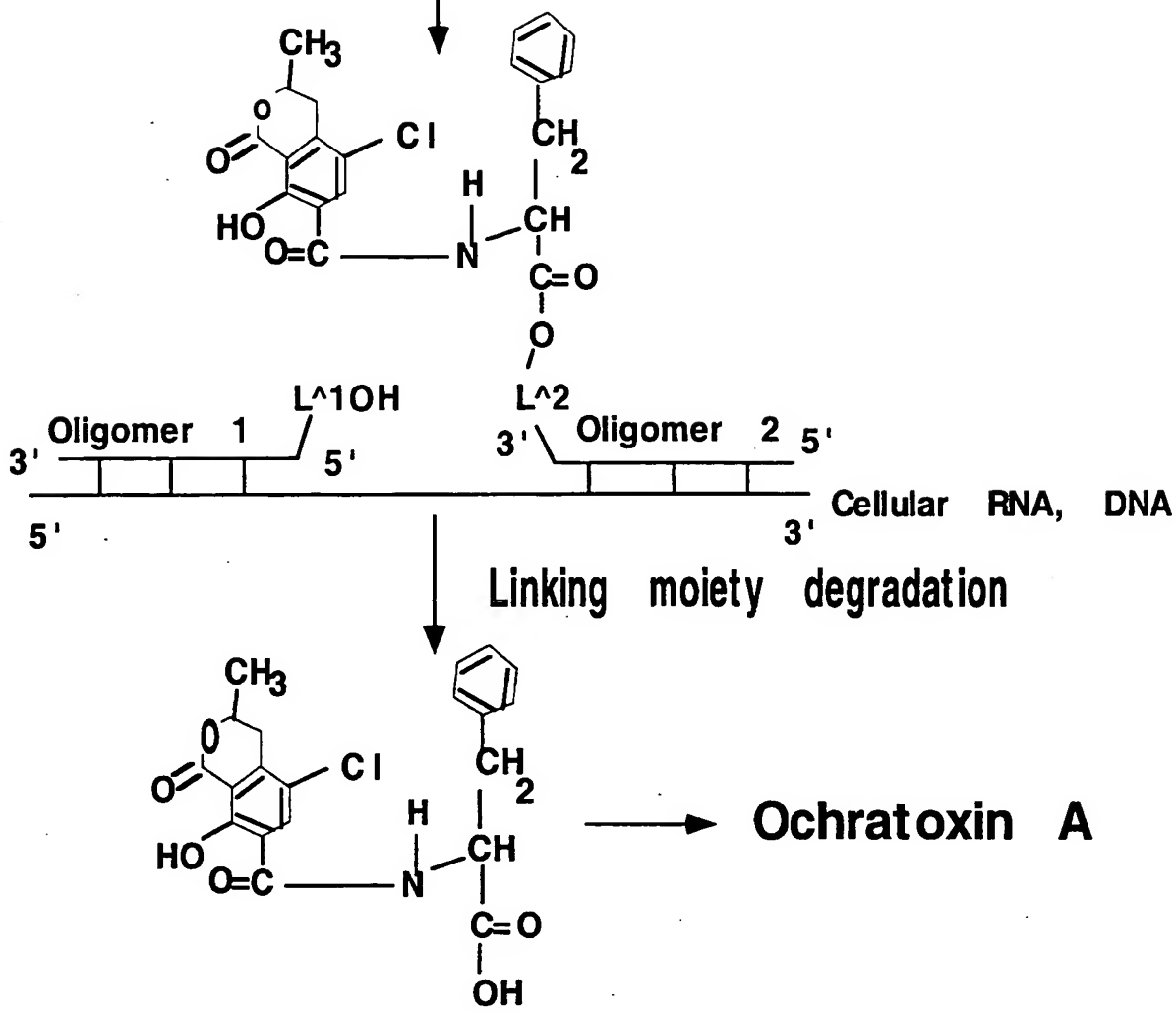

Fig. 6 continue

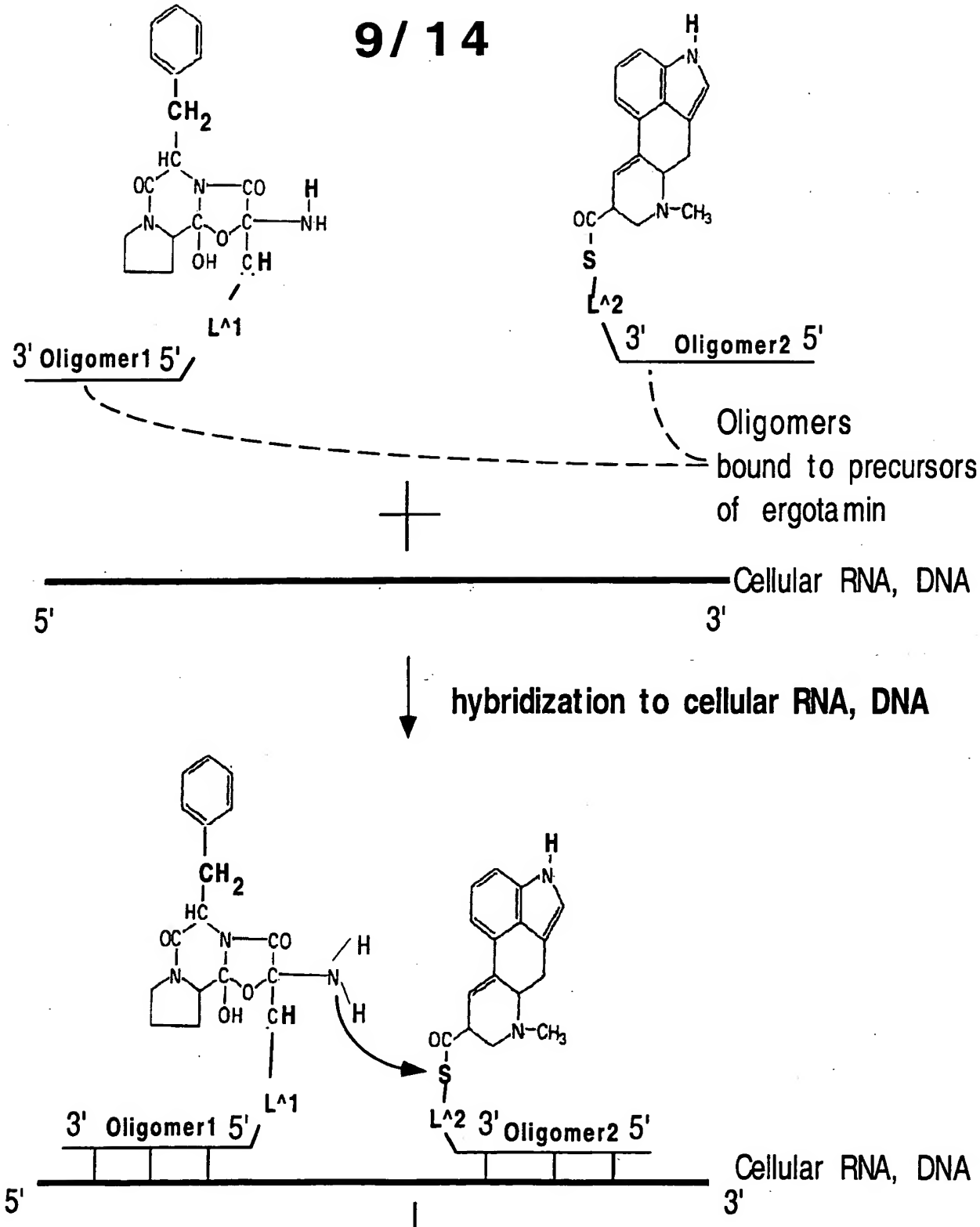
L^1
3' Oligomer1 5'
L^2
3' Oligomer2 5'
Oligomers bound to precursors of ergotamin
Cellular RNA, DNA
5'
3'
hybridization to cellular RNA, DNA
L^1
3' Oligomer1 5'
L^2 3' Oligomer2 5'
Cellular RNA, DNA
5'
3'

Fig. 7

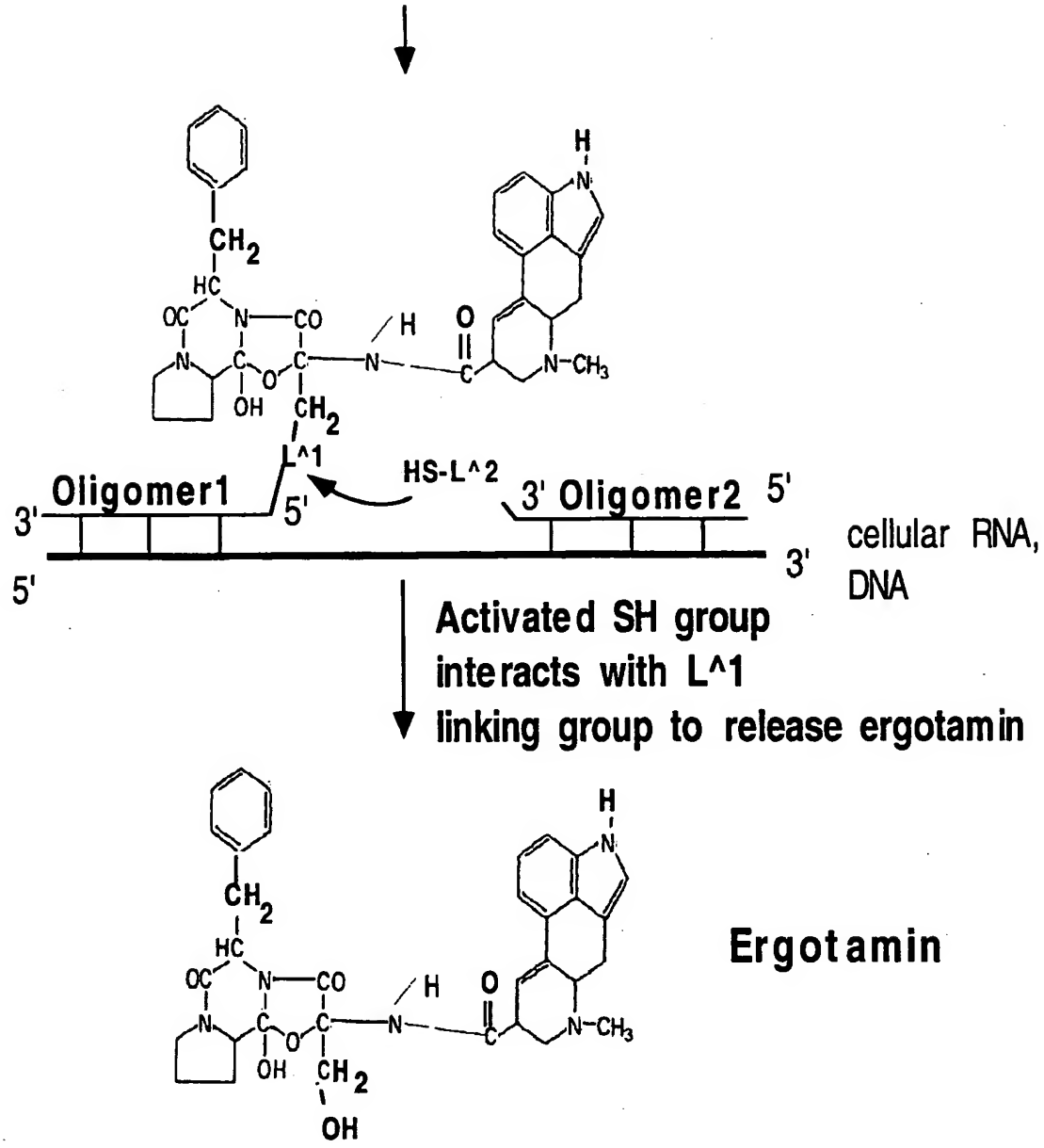

Fig. 7 continue

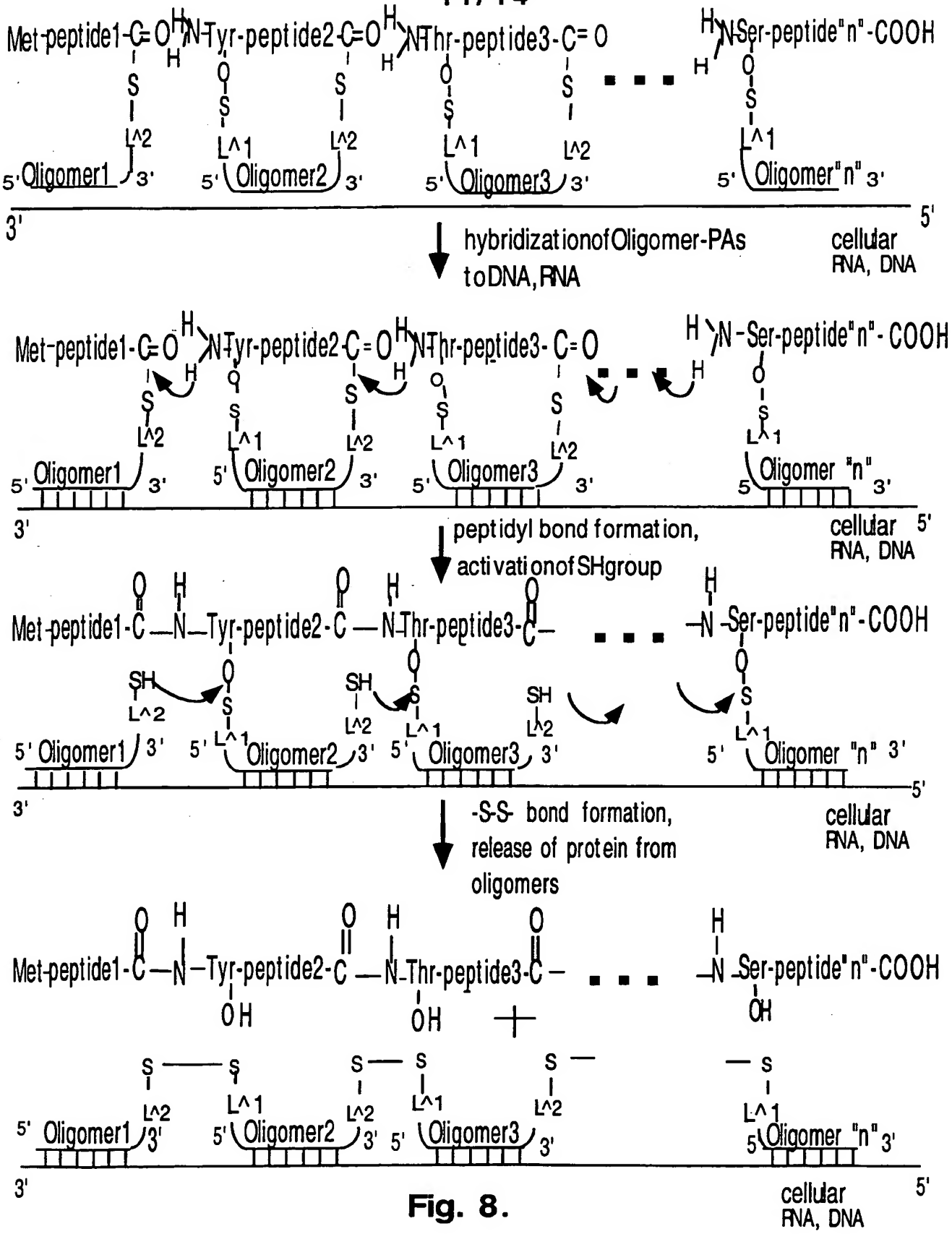
Met-peptide1-C=O
N-Tyr-peptide2-C=O
N-Thr-peptide3-C=O
N-Ser-peptide"n"-COOH
L^2
L^1
5' Oligomer1 3'
5' Oligomer2 3'
5' Oligomer3 3'
5' Oligomer"n" 3'
hybridizationofOligomer-PAs toDNA,RNA
cellular RNA, DNA
peptidyl bond formation, activationofSHgroup
-S-S- bond formation, release of protein from oligomers
OH
SH

Fig. 8.

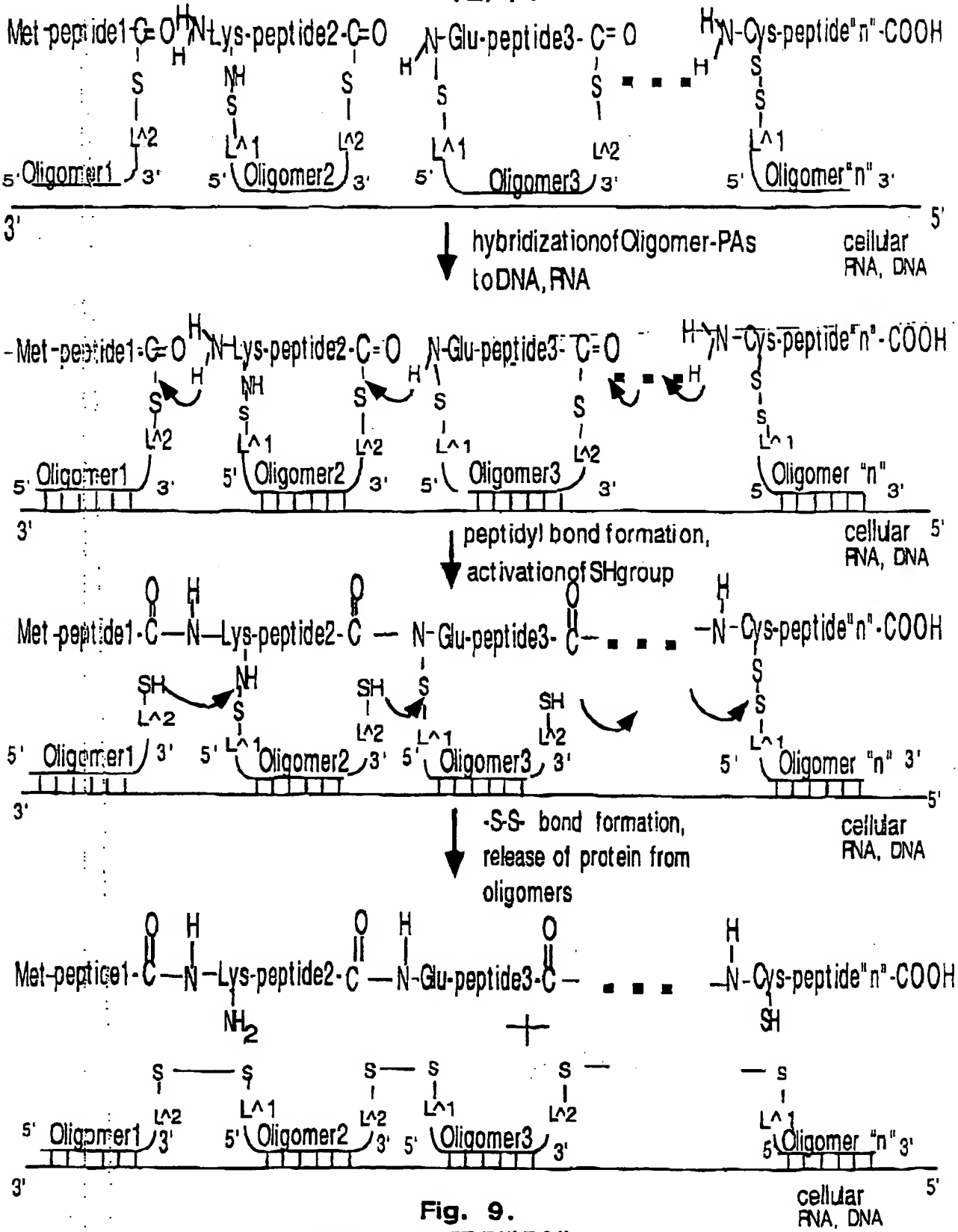

Fig. 9.

RECTIFIED SHEET (RULE 91)

ISA/EP

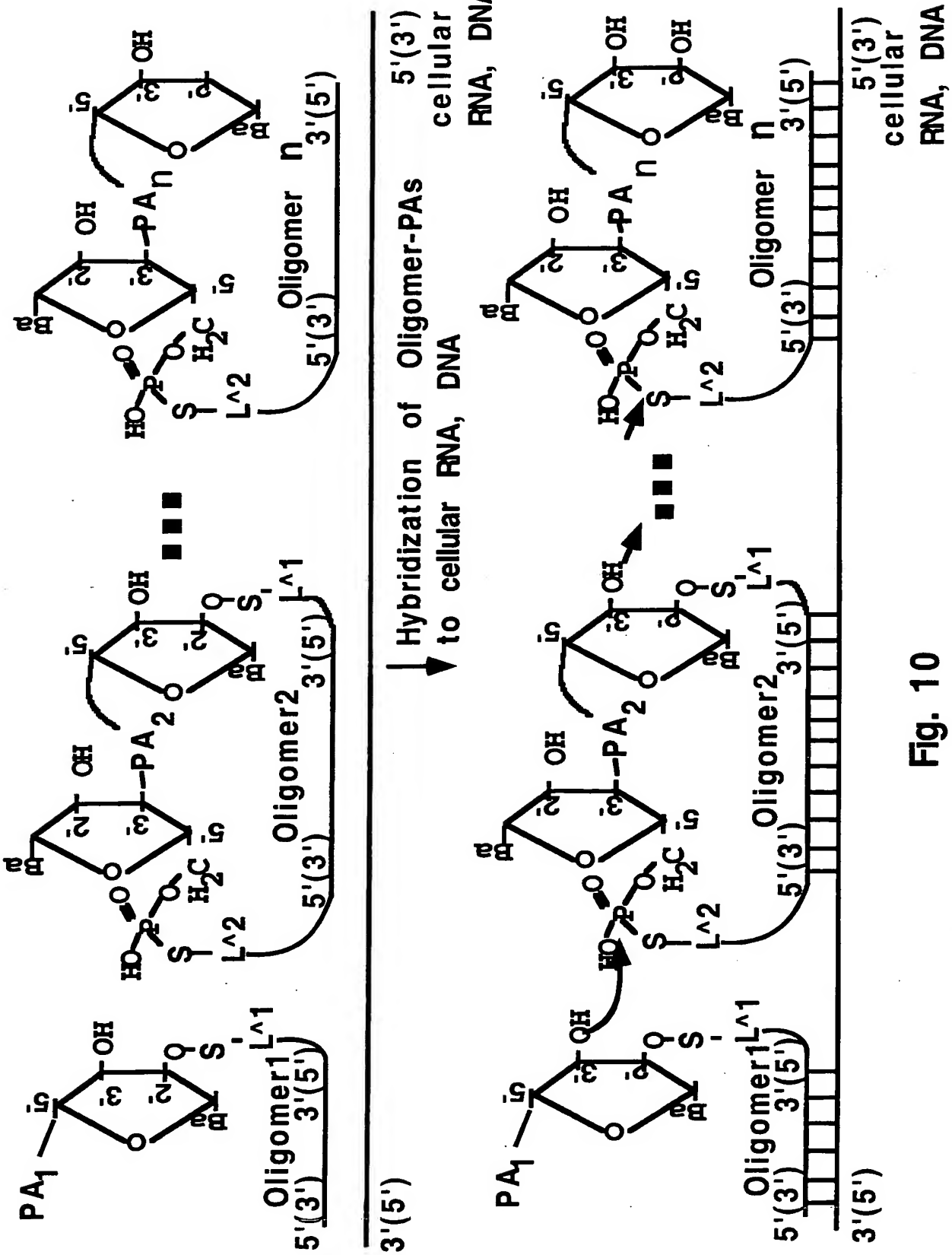
Hybridization of Oligomer-PAs to cellular RNA, DNA
5'(3') cellular RNA, DNA
3'(5')
Oligomer1
Oligomer2
Oligomer n
PA1
PA2
PAn
L^1
L^2
OH
HO
S
S-
5'(3')
3'(5')

Fig. 10

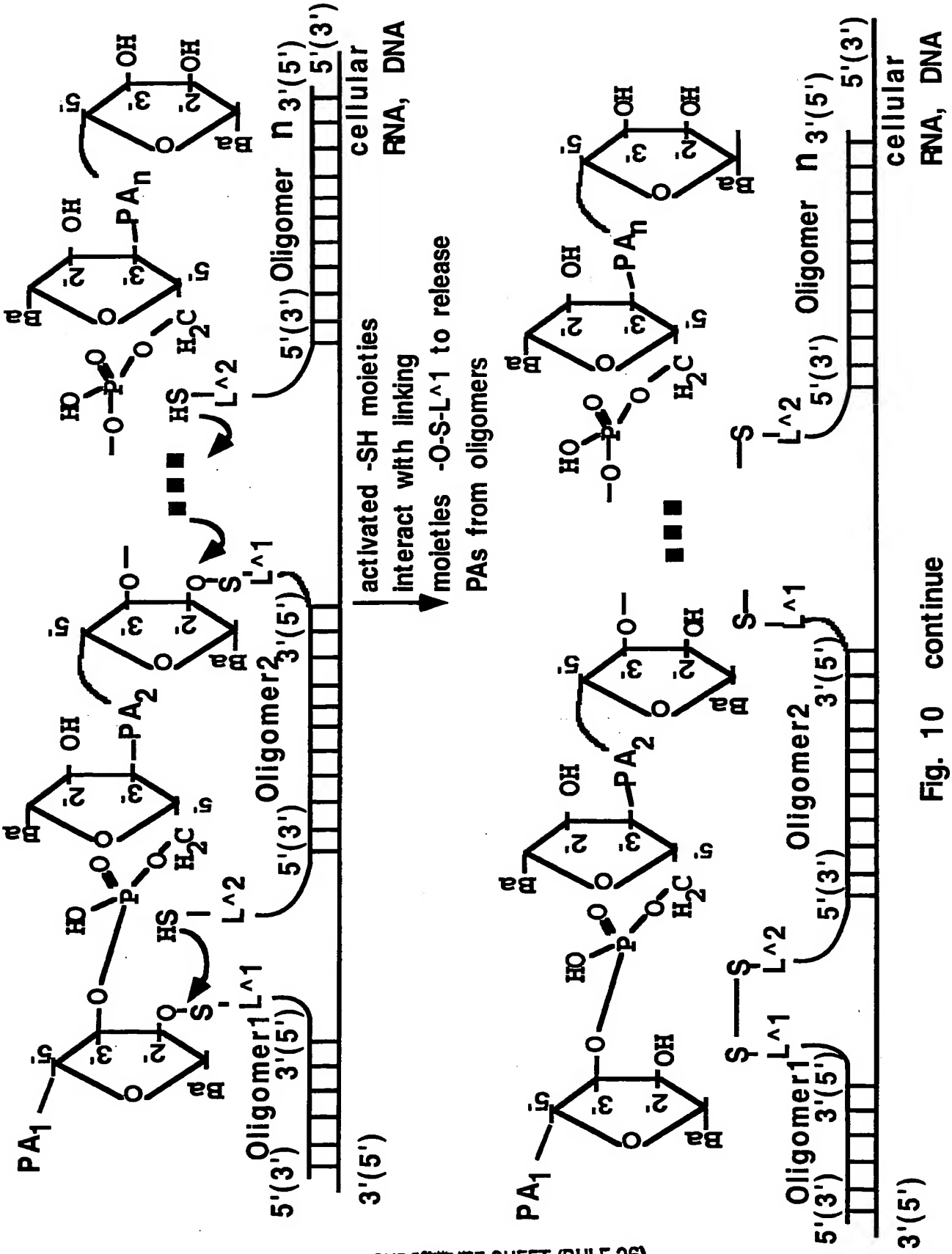

Fig. 10 continue

INTERNATIONAL SEARCH REPORT

Inter ...nal Application No
PCT/IB 99/00616

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12P1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WALDER JA. ET AL.: "Complementary carrier peptide synthesis: general strategy and implications for prebiotic origin of peptide synthesis." PROC NATL ACAD SCI U S A 1979 JAN;76(1):51-5, XP000857351 cited in the application the whole document ---	1-6,13
A	BRUICK RK. ET AL.: "Template-directed ligation of peptides to oligonucleotides." CHEM BIOL 1996 JAN;3(1):49-56, XP000856876 figure 1 --- -/--	1-6,13

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 December 1999	15/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Andres, S

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 99/00616

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	VISSCHER J. ET AL.: "Template-directed synthesis of acyclic oligonucleotide analogues." J MOL EVOL 1988 DEC-1989 FEB;28(1-2):3-6, XP000857353 the whole document	1-6,13
X	HARLOW E ET AL: "MOLECULAR CLONING AND IN VITRO EXPRESSION OF A CDNA CLONE FOR HUMANCELLULAR TUMOR ANTIGEN P53" MOLECULAR AND CELLULAR BIOLOGY, vol. 5, no. 7, page 1601-1610 XP000619201 ISSN: 0270-7306 the whole document	7,9-11
X	BUDAVARI, S. ET AL. 'THE MERCK INDEX, 12TH EDITION'; MERCK & CO., INC.; WHITEHOUSE STATION, NJ, USA, 1996, page 475 XP002124537 Abstract 2867. Dactinomycin	7,8,10
X	LIOU, Y. F. ET AL: "Antitumor agents. LIV: The effects of daphnoretin on in vitro protein synthesis of Ehrlich ascites carcinoma cells and other tissues" J. PHARM. SCI. (1982), 71(7), 745-9 ,1982, XP002124538 the whole document	7,8
X	YOSHIMOTO, K. ET AL.: "A new synthetic method for 1-O-acyl-beta-D-glucopyranoses using tri-O-trifluoroacetyl-1,6-anhydroglucose. Synthesis of tuliposode-A" TETRAHEDRON LETTERS., vol. 24, 1983, pages 2779-2780, XP002124539 ISSN: 0040-4039 the whole document	7,8
X	BUDAVARI, S. ET AL. 'THE MERCK INDEX, 12TH EDITION'; MERCK & CO., INC.; WHITEHOUSE STATION, NJ, USA, 1996, page 1159 XP002124540 Abstract 6836. Ochratoxins	7,8
X	BUDAVARI, S. ET AL. 'THE MERCK INDEX, 12TH EDITION'; MERCK & CO., INC.; WHITEHOUSE STATION, NJ, USA, 1996, page 623 XP002124541 Abstract 3703. Ergotamine	7,8

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INTERNATIONAL SEARCH REPORT

Inter. .nal Application No
PCT/IB 99/00616

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	BUDAVARI, S. ET AL. 'THE MERCK INDEX, 12TH EDITION'; MERCK & CO., INC.; WHITEHOUSE STATION, NJ, USA, 1996, pages 64-65, XP002124542 Abstract 387. Amanitin -----	7,8

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 99/00616

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 12
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

See FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 12

Present claims 7 to 12 relate to an extremely large number of possible biological active compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds prepared in the examples and defined by their chemical structure in the figures.
Therefore, as the biological RNAs claimed in claim 12 are not defined or characterised in the application, no meaningful search could be done for this claim.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.